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THE D:N RATIO IN DIABETES MELLITUS.

By Herman O. Mosenthal and D. Sclater Lewis.

(From the Medical Clinic of The Johns Hopkins Hospital.)

Minkowski,[1] observing depancreatized dogs, was the first to recognize the importance of the proportion of urinary glucose, not derived from carbohydrate of the food, to the urinary nitrogen. When the diabetic organism does not utilize ingested carbohydrate, this appears in the urine. As the disease progresses, the carbohydrate derived from protein likewise is not utilized, and appears in the urine. There is at present no convincing evidence that fat may give rise to glucose.[2] The amount of protein metabolized may be estimated from the quantity of urinary nitrogen. The ratio of unutilized glucose which is derived from protein to the urinary nitrogen, the dextrose-nitrogen, or, in short, the D:N ratio, may, therefore, be regarded as a measure of the intensity of the diabetes.

[1] Minkowski: Arch. f. exp. Path. u. Pharm., 1893, XXXI, 85.

[2] Allen, F. M., and Du Bois, E. F.: The Archives Int. Med., 1916, XVII, 1010.

1. The Maximal D:N Ratio.

Lusk[3] and his collaborators have investigated the D:N ratio of phlorhizin diabetes. They have definitely established the maximal ratio at 3.65:1, which signifies that 58.4 per cent of protein and no more is available to the organism as glucose. Very few human cases of diabetes mellitus have been observed to exhibit this maximal ratio.[4] The obstacles attending such

[3] Lusk, G.: Ergebn. d. Physiol., 1912, XII, 315.

[4] Mandel, A. R., and Lusk, G.: Deutsch. Arch. f. klin. Med., 1904, LXXI, 472.
Lusk, G.: The Arch. Int. Med., 1912, X, 122.
Foster, N. B.: Deutsch. Arch. f. klin. Med., 1913, CX, 501.
Greenwald, I.: Jour. Biol. Chem., 1914, XVI, 375; Jour. Biol. Chem., 1914, XVIII, 115.
Allen, F. M., and Du Bois, E. F.: The Arch. Int. Med., 1916, XVII, 1010.
See also Lusk, G.: The Arch. Int. Med., 1909, III, 5.

studies will be discussed in the second part of this article. Under these circumstances, even a single case is worth a great deal in establishing the true maximal ratio for human diabetes. For this reason the following record is of interest:

E. W. (Medical No. 35092), female, married, white, aged 51, was admitted to the medical clinic of The Johns Hopkins Hospital November 28, 1915. The history as obtained at the time of and previous to her fatal illness differed somewhat, as might be expected in an irresponsible individual. The main facts, however, were these:

Family and *Past History* are unimportant except for the fact that nearly every member of the family has been obese.

Present Illness: In 1899 there was thirst, loss of weight and pruritus vulvæ. Three months later, glucose was demonstrated in the urine. The symptoms cleared up rapidly with a reduction of the starchy food. She soon began to break diet; glycosuria has been present almost constantly since that time. There have been four admissions to the hospital, the last one 6 months ago, during each of which she was made sugar-free, though with increasing difficulty. Attendance at the diabetic class of the dispensary was very irregular and without therapeutic result. There has been marked loss of weight and strength. In 1899, the patient weighed about 180 pounds, although only 5 feet 4 inches in height. The present weight is 123 pounds. Four years ago she was treated in this hospital for carcinoma of the cervix; 3 years ago the growth was removed by means of the actual cautery and subsequent radium treatment was resorted to. For five years there have been sharp pains in the arms and legs, which improved on the rare occasions when an antidiabetic diet was adhered to. Three years ago, pains in the right upper quadrant of the abdomen were diagnosed as due to a movable kidney kinking its ureter. No operation was performed because of the diabetes. During this period of 5 years of suffering, the patient has had recourse to morphine, using from one-half to three grains a day. Two weeks before admission to the hospital, a bunion on the left foot became red, swollen and tender. This swelling has gradually been increasing. For the past two days there have been drowsiness and shortness of breath.

Physical Examination on Admission: T. 102.6°. P. 112. R. 26. Weight 123 pounds. Height 5 feet 4 inches. The patient is drowsy; there is a moderate degree of air hunger; the skin is dry and rough; there are numerous hypodermic scars; the skin is wrinkled, indicating the loss of much weight. The pupils are unequal; the right reacts sluggishly to light, the left is inactive. In the eyegrounds there are large patches of what appear to be exudate, most marked about the macula; a few hemorrhages are scattered over the retina. The thyroid gland is large and of elastic consistency, without a bruit or other sign of increased vascularity. The lungs are negative except for signs of a moderate grade of emphysema. The heart is negative. The liver edge is three finger-breadths below the costal margin. The spleen is not felt. In the right flank, a rather irregular mass, presumably an enlarged right kidney about 15 cm. in diameter, is felt. The left kidney is readily palpated. The knee-jerks cannot be obtained. On the dorsum of the left foot there is a sinus leading to an infected bunion; dead bone is felt on probing. The systolic blood pressure is 170, the diastolic 80. The Wassermann reaction is negative. Hemoglobin (Sahli) 77%; white blood cells, 9880; red blood cells, 4,248,000; the phenolsulphonephthalein excretion is 42% in two hours.

Course in the Hospital. The patient was starved for five days and then given very small quantities of food for the ensuing week. Her mental condition showed marked improvement, the air hunger diminished; but on the fourth day air hunger again manifested itself and continued until death. The urine at no time became sugar-free. The infected bunion showed no tendency to heal and definite gangrenous areas appeared on the sole of the foot. The patient died suddenly while sitting up and eating on December 11th. For details of the diet, administration of bicarbonate of soda, and laboratory findings, see Table I.

Autopsy No. 4530 (Dr. M. T. Burrows).

Anatomical Diagnosis: Primary: Atrophy of pancreas, with diffuse lipomatosis; hyaline islands of Langerhans. Perforating

TABLE I.

CLINICAL AND EXPERIMENTAL DATA OF E. W.

	November.			December.									
Date, 1915	28*	29*	30*	1*	2*	3	4	5	6	7	8	9	10
Urine Vol. c. c.	....	3015	3550	3500	3925	3725	3340	3600	3900	4470	4710	5940	5620
Urine Sp. G.	1021	1020	1017	1017	1015	1015	1014	1015	1015	1014	1012	1011	1012
Urine Reaction	ac.	ac.	ac.	ac.	ac.	ac.	ac.	ac.	ac.	ac.	ac.	ac.	ac.
Urine acidosis as B-oxybutyric ac., gm.	....	40.0	61.5	54.2	64.9	66.0	50.6	64.9	78.0	111.2	106.6	73.0	85.6
Alveolar CO_2 tension, mm. Hg	....	23.3	.....	35.0	.....	.....	19.5	.....	.....	.....	.....	24.6	.....
Urine, total N, gm.	....	12.4	15.6	13.0	10.2	10.8	9.8	9.0	9.6	10.5	8.9	8.7	9.9
Urine NH_3, gm.	....	2.9	4.7	4.2	4.3	4.5	4.2	3.9	4.4	4.4	4.0	4.2	3.8
Urine, $100 \frac{NH_3—N}{N}$	21.0	19.5	25.0	27.0	34.8	34.4	35.1	36.0	37.7	34.8	37.0	40.2	31.8
$NaHCO_3$, gm. by mouth	....	72	72	84	60	32	32	48	40	.....	38	.....	.....
$NaHCO_3$, gm. by infusion	....	.....	.....	.....	.....	.....	.....	14	31	32	36	40	36
Blood sugar, %	.33	.....	.....	.....	.....	.....	.....	.....	.25	.24	.....	.....	.21
Urine glucose, %	2.62	2.34	1.56	.70	.94	1.08	1.09	.88	.90	.85	.74	.60	.71
Urine glucose, gm.	....	70.6	55.4	24.5	36.9	40.3	36.3	31.9	35.1	38.0	34.7	35.7	40.0
Carbohydrate intake, gm.	....	0	0	0	0	0	2.5	6.0	2.0	3.7	3.0	3.7	14.1
Carbohydrate balance, gm.	....	—70.6	—55.4	—24.5	—36.9	—40.3	—33.8	—25.9	—33.1	—34.3	—31.7	—32.0	—25.9
D : N	....	5.69	3.55	1.89	3.64	3.71	3.46	2.89	3.44	3.28	3.58	3.68	2.62
Diet:													
Total calories	....	405	385	370	105	110	120	330	305	500	585	445	220
Whiskey, c. c.	....	100	80	90	.....	.....	.....	40	24	8	.....	.....	.....
Wine, c. c.	....	.....	.....	.....	.....	.....	.....	.....	.....	360	490	345	60
Broth, c. c.	....	500	500	400	400	400	400	500	500	500	500	500	300
Green vegetables, gm.	....	.....	.....	.....	.....	6	85	125	78	100	55	90	.....
Oatmeal (dry), gm.	....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	20
Eggs, number	.....	.....	.....	.....	.....	.....	.....	1	1	1	1	½	.....

* On these days the 24-hour collection of urine was incomplete. 500 to 1000 c. c. were lost. The volume of urine, as indicated in the table, includes the probable quantity lost. On subsequent days, not marked with an asterisk, the patient was in charge of a special nurse and the collections of urine were satisfactory.

ulcer of left foot. *Subsidiary:* Occlusion of intravesical portion of right ureter; hydronephrosis (right). Hypertrophy of left kidney. Chronic cholecystitis. Localized fibrous peritonitis. Myomata of uterus. Old operation: amputation of cervix. Pulmonary emphysema. Colloid goitre. Arteriosclerosis.

The body is that of a fairly nourished white woman. There is a considerable amount of subcutaneous fat. There is a large bunion at the distal end of the first metatarsal bone of the left foot. Between the first and second metatarsal bones there is a small perforating gangrenous ulcer. The tendon sheaths and the subcutaneous tissue of the foot bounding this ulcer are infiltrated with thick, grayish-yellow pus. The arteries are open to the edge of the ulcer where they are obliterated. The wall of the ulcer is ragged but not indurated.

The liver weighs 1700 gm. The surface is smooth except for a few adhesions to the great omentum along the inferior surface of the right lobe and in the neighborhood of the gall-bladder. The gall-bladder is small. Its wall is thickened and of a grayish color. It contains four small jagged stones and a small amount of yellowish-brown bile. There is no obstruction or partial occlusion of any of the bile-ducts.

The pancreas is much reduced in size, is everywhere infiltrated with fat; weighs 81 gm. The lobules which are present are firm.

The right kidney is a large fluctuating mass. It measures 14 x 13 cm., and although slightly lobulated, it is almost spherical in outline. The ureter is dilated, having a cross diameter of 0.9 cm. The dilatation is uniform and continuous to the bladder wall, where the ureter is completely obliterated. The kidney sac and ureter are filled with a clear fluid, which does not resemble urine, nor does it contain acetone.

The left kidney is greatly enlarged; it weighs 400 gm. The capsule is thin and strips easily. The hyperplasia as seen in this kidney is limited largely to the cortex. The cortex is thickened everywhere; it measures 8 to 10 mm.

MICROSCOPICAL NOTES.

Pancreas: The picture is that of a pronounced atrophy of the secreting epithelium of the gland. In isolated areas the gland appears normal, but in the greater part of the section the epithelial cells are decreased in size. Many acini have become reduced to a small clump of sharply staining nuclei, surrounded by a very small amount of a granular pink-staining cytoplasm. The atrophic changes are seen in every lobule and in some they are extreme. Whole lobules have become reduced to small contracted masses of connective tissue in which only the ducts can be identified. The same changes are seen in sections from the head, body and tail of the pancreas. In none is there any evidence of an increase of fibrous tissue, but rather a shrinking together of the original fibrous tissue. The increase of fat, noted on inspection, is only an apparent increase following an extensive atrophic change. The islands of Langerhans show no atrophy but an extensive hyaline degeneration. The cytoplasm of the cells stains pink and is visibly granular. The nuclei are absent in many cells, and when present are shrunken and vesicular and irregular. The nuclei of the endothelial lining of the blood sinuses are intact. In the great majority, however, the cells have become completely and uniformly hyaline. The stain is a distinct pink color. The endothelial cells of the sinuses are swollen and stand out prominently; many have degenerated into the lumen of the sinuses. The nuclei of many are pycnotic and in some cases shrunken and vesicular in shape. A few of the islands are breaking down; along the sinus walls there are vesicles in which are many picnotic nuclei, surrounded by a small amount of cytoplasm.

Throughout these studies, the nitrogen was determined by the Kjeldahl method, the urinary ammonia by Steel's modification of Folin's method,[5] the urinary glucose by Benedict's modification of Fehling's solution,[6] the acetone substances in the urine by Shaffer's[7] procedure, the blood sugar by the method of Lewis and Benedict,[8] the tension of carbon dioxide in the alveolar air, in samples collected by the Plesch method as modified by Higgins,[9] by Haldane's[10] method for gas analysis; and the food values were calculated from the tables of Atwater and Bryant,[11] with a few exceptions in which we made our own analyses.

All the data in the case of E. W. point to the fact that this patient is suffering with a diabetes of maximal severity. The height of the D:N ratio indicates that no glucose from either carbohydrate or protein is being utilized. The large quantities of acid substances excreted in the urine surpass in amount, at least during the last few days of the illness, the maximal yield of about 35 per cent[12] which can be obtained from protein. Hence, some of the β-oxybutyric acid must have its origin from both fats and proteins. It is evident that in this instance the calories ordinarily derived from starch and protein are entirely lost, those from the fats are partially made use of, and only those from the alcohol are completely metabolized. Under such circumstances, it is probable that death resulted from starvation, not because of inadequate nourishment (there was a considerable amount of subcutaneous fat), but because of inability to utilize the food offered to the tissues.

The fasting treatment of Allen did not prove itself efficient in this instance. This may be explained on the double ground of the infected bunion and of the maximal diabetes. Joslin[13] noted that intercurrent infections frequently frustrated the efficacy of the fasting treatment. Allen and Du Bois[14] find that the few known cases which have exhibited the maximal D:N ratio during fasting have died, except the patient of Geyelin and Du Bois.[15]

The D:N ratios in the present case were so close to the ideal maximal ratio of 3.65:1, in eight of the 12 days observed, as to be considered identical with it. The high ratio on the first day is readily explained by the fact that carbohydrate, which had been previously stored during a period of lax diet, was eliminated. The low ratio on the last day is a typical result of feeding carbohydrate—oatmeal in this instance. Such a lowering of the ratio under similar circumstances has frequently been noted and up to the present time has not been

[5] Steel, M.: Jour. Biol. Chem., 1910, VIII, 365.

[6] Benedict, S. R.: Jour. Am. Med. Assn., 1911, LVII, 1193.

[7] Shaffer, P. A.: Jour. Biol. Chem., 1908, V, 211.

[8] Lewis, R. C. and Benedict, S. R.: Jour. Biol. Chem., 1915, XX, 61.

[9] Higgins, H. L.: Publication No. 203, Carnegie Institution of Washington, 1915, p. 168.

[10] Haldane, J. S.: Methods of Air Analysis, London; Chas. Griffin & Co., Ltd., 1912.

[11] Atwater and Bryant: U. S. Dept. of Agriculture, Bull. No. 28, 1906.

[12] Magnus-Levy, A.: Ergebn. d. inn. Med. u. Kinderh., 1908, I, 352.

[13] Joslin, E. P.: "The Treatment of Diabetes Mellitus," Philadelphia and New York, 1916, p. 267.

[14] Allen, F. M., and Du Bois, E. F.: The Archives Int. Med., 1916, XVII, 1010.

[15] Geyelin, H. R., and Du Bois, E. F.: Jour. Am. Med. Assn., 1916, LXVI, 1532.

satisfactorily explained. The ratios of 1.89:1 and 2.89:1 on the third and seventh days respectively are considerably lower than the theoretical maximal ratio. A discussion of the possible factors concerned will be taken up in the second part of this article. However, these partial exceptions do not invalidate the conclusion that the D:N ratios in this patient approximate the maximal ratio of Lusk—3.65:1—as closely as it is possible for a clinical observation to approach the fully controlled laboratory experiment. The contention that 58.4 per cent of protein and no fat is available to the human body as glucose is substantiated.

2. The Factors on Which the D:N Ratio Depends.

Very many reasons have been brought forward to explain the very variable D:N ratios in some cases of human diabetes. The most important of these have been the possibility of previous or present storage of sugar or glycogen, the fact that the nitrogenous and the non-nitrogenous portions of the protein molecule are not excreted with equal rapidity in the urine, the tendency of ingested carbohydrate, as in the oatmeal cure, to lower the ratio, and in instances of lax diet to raise it. These subjects are ably discussed by Joslin,[16] and Benedict and Joslin [17] in monographs in which they point out the impossibility of obtaining reliable D:N ratios in most cases. To sum up the situation, there is not much to be added to the statement of Rumpf,[18] made some years ago, that "The intensity of the glycosuria is entirely independent and is uninfluenced by any known causes."

The essential difference between phlorhizin diabetes, in which constant D:N ratios are readily obtained, and human diabetes, in which they are not, is that the glycosuria in the former depends upon an increased permeability of the kidney to glucose, whereas in the latter, a metabolic disturbance, an inability to utilize glucose, is at fault. The relation of the permeability of the kidney to the glucose of the blood in diabetics is a question which has received but scant attention thus far. However, even the few facts gleaned at the present time indicate that this relationship is not a fixed one and consequently may result in varying levels of the D:N ratio.

In some cases of diabetes sugar does not appear in the urine, though the level of glucose in the blood surpasses the normal renal threshold of about .1%.[19] This is well illustrated in Table II. Such a state is not necessarily confined to nephritis, as is often assumed, but may be brought about by other factors concerning which little is known. Martin and Mason [20] have recently reported similar findings. In fact, one case (Table IV), to be detailed further on, shows how nephritis is not necessarily associated with a diminished permeability of the kidney to glucose, but may even exhibit a lowered renal threshold.

[16] Joslin, E. P.: The Archives Int. Med., 1915, XVI, 693.

[17] Benedict, F. G., and Joslin, E. P.: Carnegie Institute of Washington, Publication No. 136, 1910, pp. 197-201.

[18] Rumpf, T.: Ztschr. f. klin. Med., 1902, XLV, 260.

[19] Hamman, L., and Hirschmann, I.: To be published.

[20] Martin, C. F., and Mason, E. H.: Am. Jour. Med. Sc., 1917, CLIII, 50.

TABLE II.

Glycemia Percentage in Diabetics, Showing a Blood Sugar of .20% or Higher, While the Urine Was Free From Sugar.

Case 1	.20				*Case 9	.22			
Case 2	.20	.20			Case 10	.24	.22		
Case 3	.20				Case 11	.25	.21		
*Case 4	.20				*Case 12	.25			
Case 5	.20				Case 13	.27			
Case 6	.21	.20	.20		Case 14	.28	.20		
Case 7	.21				*Case 15	.31	.27	.25	
*Case 8	.21				Case 16	.32	.30	.21	.20

* These gave clinical evidences of nephritis; the remainder did not.

Such a raised renal threshold to glucose need not be permanent, as may be seen from Table III, which shows data from a case in which the urine contained no glucose, while the blood sugar was as high as .237%, whereas some time later sugar was excreted with a glycemia of .180% or less.

TABLE III.

Data Demonstrating the Variability of the Renal Threshold to Glucose in a Case of Diabetes Mellitus.

Time.	Blood sugar.	Urine.		
			Glucose.	
	%	c. c.	%	gm.
Nov. 11	.237	24-hour specimen.	0	0
12	.220	24-hour specimen.	0	0
13	.180	24-hour specimen.	0	0
Dec. 1				
11.00 a. m.	.177			
12.19 p. m.	.180			
10.45 a. m. to 12.27 p. m.		70	.36	.25
3.35 p. m.	.161			
4.46 p. m.	.181			
3.36 p. m. to 4.48 p. m.		96	.40	.38
Dec. 8				
9.30 a. m.	.173			
10.25 a. m.	.142			
9.33 a. m. to 10.27 a. m.			+	+
11.30 a. m.	.180			
10.27 a. m. to 11.32 a. m.			+	+

Finally, to complete the list of possible variations, the data from a case showing a distinctly lowered renal threshold may be cited (Table IV). This patient resembled in many respects the one with renal glycosuria recently reported.[21] However, one very essential difference is apparent. The present study reveals a blood-sugar curve after the administration of 100 gm. of glucose which is characteristic of diabetes mellitus, or possibly of nephritis,[22] but not of a normal person. The blood sugar rises as high as 0.26 per cent (normal 0.15 per cent); it attains its maximum only at the end of one hour (normal 15 to 30 minutes), and does not return to the fasting level for three hours (normal two hours).

The more important clinical data in this patient are:

S. B., medical history No. 36823, white, age 63. He had been treated in the out-patient department for some time, the diagnosis being chronic nephritis and hypertension; the fourth urinary examination revealed the presence of a small amount of glucose.

[21] Lewis, D. S., and Mosenthal, H. O.: Johns Hopkins Hosp. Bull., 1916, XXVII, 133.

[22] Hamman, L. F., and Hirschmann, I.: To be published.

Fehling's reaction and the fermentation test were both distinctly positive; the blood sugar at the time this specimen was passed was only 0.11%. He was admitted to the hospital for investigation; a partial result of the studies is given in Table IV. It was demonstrated that a renal glycosuria was present, and at the same time the blood sugar reaction, after the ingestion of 100 gm. of glucose, indicated a metabolism characteristic either of nephritis or diabetes mellitus; there was abundant evidence of the presence of a nephritis, with a considerable degree of diminished renal function; the urine contained a trace of albumin and a few hyaline and fine and coarse granular casts; the specific gravity had a tendency to be low and fixed, as shown by the test meal for renal function and the daily urine specimens as well; the phenolsulphonephthalein excretion was 22 per cent in 2 hours, the urea nitrogen of the blood 35 mgm. per 100 c. c., and Ambard's coefficient of urea excretion 0.17. All the peripheral arteries were moderately thickened; ophthalmoscopic examination was negative except for somewhat tortuous arteries; the systolic blood pressure varied between 170 and 160 mm. of mercury, the diastolic between 100 and 90; the heart was slightly enlarged to the left, the apex beat being in the fifth space, 11.5 cm. from the median line. The final clinical impression was: Arteriosclerosis, primary contracted kidney of fairly advanced degree, hypertension, renal glycosuria, and possibly a mild diabetes mellitus.

TABLE IV.

BLOOD-SUGAR DETERMINATIONS AND DEGREE OF GLYCOSURIA AFTER 100 GM. OF GLUCOSE IN S. B.

	Fasting.	After 100 gm. of glucose.							
		15 min.	30 min.	45 min.	1 hour	1 hour 30 min.	2 hrs.	3 hrs.	4 hrs.
Blood sugar, %.....	.10	.15	.18	.23	.26	.26	.23	.10	.07
Urine glucose, %.....	.13	.13	.37	.80	1.61	3.33	2.00	1.11	.33

There is a distinct lowering of the kidney threshold for glucose, and a marked exaggeration of the blood-sugar curves both as regards the level to which it rises and the duration of the hyperglycemia. This, therefore, is a case of renal glycosuria, associated with chronic nephritis (see clinical data), and possibly diabetes mellitus as well.

The conclusions in regard to this case are that this is an instance of increased renal permeability to glucose, associated with a distinct nephritis, and possibly with diabetes mellitus as well.

One final factor must be considered in explaining the varying intensity of glycosuria under apparently constant conditions. The reaction of the blood sugar to meals in any individual is not constant. Graham [23] attributed such changeable findings in health to fatigue. Similar variations occur in diabetics for no apparent reason (Table V). A more marked glycosuria would be expected to follow a blood-sugar curve such as is shown on December 1st than on either December 8th or 15th. The cause for these changing results is not clear, since this patient was on a carbohydrate-free diet of 1700 to 2000 calories for some time before as well as during the observations. Furthermore, the initial blood sugar was always taken while the patient was fasting, that is, before breakfast, and the meal was identical in each instance.

[23] Graham, G.: Jour. Physiol., 1916, I, 285.

TABLE V.

BLOOD-SUGAR DETERMINATIONS IN A CASE OF DIABETES MELLITUS, AFTER A CARBOHYDRATE-FREE MEAL OF THE SAME WEIGHT AND KIND OF FOOD IN EACH INSTANCE.

Date.	Blood sugar per cent.															
		After a carbohydrate-free meal, of the same weight and kind of food on each date.														
	Fasting.	14 min.	15 min.	25 min.	32 min.	46 min.	50 min.	1 hour 15 min.	1 hour 19 min.	1 hour 30 min.	2 hours 2 min.	2 hours 33 min.	3 hours 5 min.	3 hours 30 min.	4 hours.	4 hours 41 min.
Dec. 1.....	.177	.180	....	....	....	.225	....	....	.225	....	....	.192	....	.161	....	.181
8.....	.173	....	....	.142	....	....	....	....	....	.180	....	....	....	....	....	....
15.....	.072	....	.065	....	.065	....	.090	.086	....	....	.094	....	.110	....	.106	....

The results are very unlike each other, although this patient was kept in a small ward in the hospital during the period of study, under constant conditions of diet and hygiene.

Although these few experimental data do not exhaust these subjects, which are still under investigation, they show that the renal threshold to glucose undergoes great changes, and that the rise of sugar in the blood after meals differs greatly at intervals under apparently similar conditions. It is believed that these two factors, in addition to those previously mentioned, are largely responsible for the changing level of the D:N ratios often noted in well regulated cases of diabetes.

CONCLUSIONS.

1. The data of a case of diabetes mellitus demonstrating a maximal dextrose nitrogen ratio of 3.65:1 are presented.

2. Among the principal causes for apparently spontaneous changes in the D:N ratios present in some cases of diabetes mellitus are: (1) the inconstant renal threshold to the blood sugar, and (2), the variable heights to which the blood sugar rises after meals, even though these are not appreciably modified from day to day.

THE NATURE OF RESISTANCE TO TUBERCULOSIS.[1]

By ALLEN K. KRAUSE, M. D.

(From the Kenneth Dows Tuberculosis Research Fund of the Medical Clinic of The Johns Hopkins Hospital.)

As our insight penetrates deeper and deeper into recesses that were once dark to us we consciously or unconsciously demand more precise description of terms to denote phenomena that obtrude upon our senses, but defy our understanding. Upon first appreciating a thing, be it light or sound, an abnormal sensation or an unusual conformation of the body, we give it a name. But we are mentally so endowed that we are not long content with the mere name of a thing. We must know where and how it begins and ends, and through what media it works: we must discover its attributes and, these determined, we must enlarge and refine our definition

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and description. With more precise definition and description comes the conception that nothing that we sense is isolated or autogenic. It is born of something and brings forth something. And once our minds begin to deal with its causes and effects then we can say that the thing has entered into our understanding. Then only can we affirm that its name is to us perhaps something more than a mouthful of words.

Terminology, description and a knowledge of cause and effect—every domain of knowledge, every phase of science passes through these three stages on the road from sensation to reason; and medicine, the all-embracing, the focus of all sciences, the handmaid of mathematics, physics, chemistry, botany, climatology, sociology and psychology, is to-day perhaps in all three stages. A genius, a Helmholtz, arises and lays bare the mechanism of the eye. A Richard Bright, a Louis or a Gerhard sifts, describes and clarifies a confused mélange. A man with a knack for observation, perhaps a dermatologist, classifies those things that are red, or those that are raised, or those that itch, or those that appear on certain parts of the body: and he thereby really brings under control his science and takes a step far beyond the time when he called everything a "humor" or a "tumor." But terms, mere terms, persist, and are too often accepted as explanations. Nephritis, cardio-nephritic, myocarditis, arteriosclerosis, hypertension, hypertensive-nephritic, myocardial insufficiency with hypertension, hypertension with renal insufficiency: what a real evolution of knowledge these terms convey, yet how little more than terms they are! Naming much and describing some things they explain nothing.

I feel very diffident in coming before you to-night and talking about what has often seemed to me to be, as commonly used, a mere term or symbol. I have attended clinics given by some of our best men and have heard the affirmation that a liberal diet of milk and eggs would increase the tuberculous patient's resistance. I have seen the specialist impressively produce his syringe and just as impressively assure the patient that a prolonged course of tuberculin therapy would further the latter's resistance. Time and again I have read that a man overcame his tuberculosis because his resistance improved or that he declined because he had no resistance. And hearing these statements I have often wondered just what was going through the man's mind when he talked about resistance. Did he mean anything or, if he did, had he any conception of what he tried to express? Or did he merely wish to avoid mental exertion and therefore seek to explain an effect by a handy word?

If there is such a thing as resistance to tuberculosis, then we must mean that the human body can protect itself in such a way that the tubercle bacillus, a parasitic invader, can gain no foothold or make but limited headway in it. We must assume further that under the influence of a specific irritant, the bacillus, the body reacts in a particular manner. So long as it reacts sufficiently to prevent the invasion or spread of the tubercle bacillus just so long we would say that resistance is satisfactory. If, however, it fails to do so, then resistance is lowered or absent. The entire relation of the tubercle bacillus with the animal organism is one of reaction. Vivre c'est réagir: to live is to react; and from conception to final dissolution man's vital history is nothing but an unceasing period of countless myriads of reactions that go on simultaneously or unfold themselves in sequence. We must look upon every reaction to a potentially harmful stimulus or irritation as an effort at protection and adaptation. The body reacts to the rays of the sun in a certain definite manner and thus protects itself against them. It reacts to the introduction of pork or morphine in wholly different ways and thus adapts itself to them. It reacts to the implantation of the tubercle bacillus in a very particular manner and meets the germ with the formation of a special type of cellular accumulation which we call the tubercle. These are trite though fundamental conceptions of biology. In thinking of any tissue or organic attributes like resistance we dare not forget them, and it is likely that during the next few minutes I shall recur to them again and again. To live is to react. And, if the stimulus or irritant be one that is disagreeable to tissue, then to live is to resist. Whether resistance to a given irritant at any given time is adequate enough is another matter, yet it is certainly true that if we are to live, then we must resist. Therefore, in addition to the three necessary attributes of assimilation, motion and reproduction, as they are generally given for protoplasm, I would add a fourth attribute, resistance. I am aware that this fourth attribute may be partly contingent on others such as assimilation and motion, but it is conceivable that in highly organized animals resistance goes on independently of them.

We assume, therefore, that there is a resistance to the tubercle bacillus, but in thus stating the proposition we have got little beyond giving a name to the known fact that tissues react to tubercle bacilli. We have not explained or illuminated a single thing. It is my purpose to-night to inquire into the nature of this resistance, to attempt to discover how it acts and what are its effects. I trust that you will be tolerant with me while I lead you into regions which, I know only too well, are strewn with obstacles and beset with pitfalls.

Let us first look into what happens when tubercle bacilli are taken into the body for the first time. Let us take for granted what happens in the vast majority of cases, that is, that they enter by the mouth or the nose. After excursions of varying lengths they come to rest. They may be caught in the vibrissæ of the nose, on the moist surfaces of the tortuous nasal passages or in the mucus of the nasopharynx, and be almost immediately blown out or expectorated with the nasopharyngeal secretion. Here at the very beginning we meet with a protective mechanism at the body's command.

But let us assume that they get further and penetrate the mucous membrane of the tonsil or pass into the submaxillary glands or go further down into the larynx and reach the deep cervical glands. They are now no longer *on* an epithelial surface where they cannot produce an effect: they are *in* tissue. What happens now? The tissue reacts. Fixed tissue cells of connective tissue (mesoblastic) type begin to show agitation and unrest. Their nuclei swell, chromatin rearranges itself

and heaps up in a bizarre manner, the cells themselves enlarge and in a short time we find that they are dividing, multiplying and heaping up, and surrounding and englobing the offending parasites. Now, too, cells begin to slip in from the circulation. Leucocytes accumulate in this new, round, globoid speck of matter and a tubercle comes to view. A few more days go by, and we meanwhile study the life cycle of this tubercle from time to time. What do we find? We notice developing under our eyes an avascular growth or formation of tissue, surrounding and englobing the parasitic invaders and shutting them off from the rest of the body. The bacilli are held within a globular, bloodless wall. So long as the wall is competent, so long as circulation between the interior and exterior of the tubercle is at a minimum, so long as the fibrous wall of the tubercle holds against invasion by bacilli from within or a flooding of body fluids and a consequent softening from without, just so long will the body have the germs in this initial tubercle under control.

Fortunately for most of us this is the extent of our more intimate and involuntary acquaintance with the tubercle bacillus. We are infected but without clinical disease. We have tubercle but not tuberculosis. And once having tubercle, it may be that with never a symptom of specific illness we will go through a long life without ever thoroughly eradicating the tubercle bacilli from our bodies. Though this statement cannot be proved, all our knowledge points to the fact that once having gained entrance to an animal body and once having developed sufficiently to arouse tubercle, the bacilli are never completed wiped out. Why, then, when all of us are infected, are so few of us ill? Where does resistance begin, what does it consist in and how far does it go? For surely there must be some resistance, or otherwise the bacilli would multiply and spread through us like wildfire. Under the very special premises that I have outlined, is there a resistance to infection or implantation or is the resistance merely to subsequent invasion? Has any man or animal a native resistance to initial infection by a type of tubercle bacillus to which his kind is susceptible?

We know that several diseases do not decimate civilized communities in the way in which they cut down primitive peoples. Measles and tuberculosis are real plagues if introduced among the Esquimaux and the dwellers of the South Sea Islands, but to-day occur as relatively benign diseases among peoples who have a long history of community life behind them. For this reason we postulate and teach that some nations have developed a racial immunity to tuberculosis and measles. This may be true to a certain extent, but this racial resistance is not a resistance to infection. If exposed, practically every child on earth to-day develops measles and practically every human being reacts with tubercle. In other words, all become infected; and we cannot assume that there is any racial resistance to implantation of the micro-organism. Again, if an individual is not tainted with tubercle, we cannot by any known method demonstrate that he harbors substances that may be antagonistic to the tubercle bacillus. And, if we treat an animal by certain procedures we may find in his blood certain bodies like agglutinins, aggressins, precipitins and opsonins, yet unless we give the animal anatomic tubercle it will not be more resistant to infection than any other non-infected animal that has not been thus treated. Because of these facts we must assume that man and animals have no native racial resistance to infection by tubercle bacilli in the sense that born in them is some substance or substances that specifically destroy or neutralize tubercle bacilli that seek an entrance. But there is a difference between the way in which the tissues of the Jew meet the onslaught of the tubercle bacillus and that in which the tissues of the Esquimaux meet it. There is a difference between the reaction of the tissues of the new-born infant and those of the city-dwelling adult to bacillary implantation. Both the time and character of these reactions are different. The tubercles develop differently and this difference of development in large part determines the issue. Remember that tubercle formation is response to irritation, be the irritant a hair, a grain of sand or a living, self-propagating, parasitic tubercle bacillus containing, as it does, a very high percentage of fats and waxes that are got rid of by the body only with great difficulty. This reaction is resistance, and an attempt on the part of the body to isolate or wall off the foreign body. Remember that, inasmuch as all of us become harborers of tubercle, we must assume that there is no native *increased* resistance to infection by tubercle bacilli. Remember, too, that as tissues become infected their capacity to react changes.

Let us now consider for a moment what I choose to call the mechanical element in resistance to tuberculosis. I have often wondered why pathologists have not paid more attention to the architecture of the tubercle as a formation designed by its very structure to resist further invasion by the tubercle bacillus. To me the most impressive feature of a tubercle is the fact that here we have a wall built around a foreign body, that the wall is formed around the foreign body to encyst it and render it innocuous to the infected organism, that, as long as the wall holds, the germs cannot get out and spread throughout the organism and that a necessary condition to the competence of the investing wall is fibrosis and a minimum of circulatory give and take between the center of the tubercle and the tissue that surrounds it. We can go even further. We can affirm that to produce symptoms of disease the tubercle must give up something in itself to the body, that the latter must absorb this material if it is to suffer symptoms of illness, that it can absorb something from the tubercle only if there is again a sufficient circulatory give and take between it and the tubercle, and that the circulatory exchange between tubercle and infected organism will be directly proportionate to the degree of fibrosis or sclerosis of the investing wall. Thus, resistance to further spread of bacilli and freedom from symptoms are to be understood not in terms of the body producing some fighting units which go out to battle with the germs or to neutralize their poisons. They are to be understood as being simply the result of a mechanical barrier which the body interposes between itself and the parasite.

Suppose a man has such a tubercle in his lung in close proximity to a blood vessel. It has never made itself manifest. The man has always been in perfect health. In perfect health he runs a hard race or plays a fast tennis game. Like a bolt from the sky a pulmonary hæmorrhage strikes him down, and immediately he falls ill. Another man leaves home in the morning feeling perfectly well. Suppose that for years he has had a slow and sluggishly progressive tuberculous process in a bronchial gland, yet has never had a symptom from it. Suppose further that while he is at his desk the last tenuous sheath between this caseous gland and the lumen of his bronchus is broken through, perhaps because of coughing or some sudden muscular effort. And suppose that the contents of this diseased gland are discharged widespread into the bronchus. Such a man comes home in the evening sick, with beginning caseous pneumonia.

Suppose now that for years a small gland has lain close to the thoracic duct and that firmly shut within its capsule there has smouldered tubercle. But the time comes when the tuberculosis ulcerates into the thoracic duct and from perfect health a man is precipitated into generalized miliary tuberculosis.

What shall we say about such patients? Shall we say that they developed acute tuberculosis because their resistance gave way? Yes, we may say so. But what did their resistance consist of? In these cases resistance certainly meant that foci of infection and disease were isolated and shut in by barriers of tissue and that when the barrier went resistance went.

Let us take another instance. Here is a tubercle in the lung, with bacilli well shut in and wall thoroughly competent under ordinary conditions, and its possessor a thoroughly healthy man. He develops a common cold or a bronchitis and soon after presents symptoms of tuberculosis. In terms of resistance how shall we view the onset of his tuberculosis? I have often heard just such cases explained in terms something like this: that the acute respiratory disease lowered the man's resistance, that he was left in a run-down condition, that the cells of his body therefore lay more open to invasion by the tubercle bacillus. I shall not pay detailed attention to the lack of precise reasoning in such an explanation. But I should like to put forth one that is much more plausible, and, I believe, deals more with physiological facts. Is it not more likely that during the man's "cold" or bronchitis there was a certain amount of congestion of the affected tissues, that this congestion extended to the neighborhood of the tubercle and that it established new channels of communication and circulation between the tubercle and the surrounding tissue, unlocking or opening the capsule and allowing a fresh dissemination of interned bacilli? If hard exercise will produce the circulatory conditions necessary to break through an old tubercle and thus cause unlooked-for hæmorrhage, why will not congestion about a tubercle exert a more or less similar effect? Here again resistance is a matter of simple mechanics. The patient is as resistant as the shell of his tubercle.

Hard physical exercise, sudden and intense muscular exertion, a cough, a common cold, childbirth, tuberculin in overdose, alcohol, all can produce the same circulatory effect in the neighborhood of the tubercle and, theoretically at least, can bring about the same result, a better circulatory give and take between the tubercle and the host, with a recrudescence of symptoms or a mobilization of bacilli or both. This may be momentary or it may be prolonged. If the inflammatory stimulation is not overdone, proliferation and repair will soon set in, and good may result. If it is too intense, then dissemination and progression of disease may ensue. But there is no doubt that some part of what we have been accustomed to call resistance to tuberculosis is more or less bound up with the mechanics of the circulation around the tubercle.

The body responds to exercise in a very definite way: the pulse rate and pressure rise and the respiratory activity is increased. It is not difficult to imagine how under these circumstances the lungs are affected and what might happen to an old encysted tubercle. We recognize this fact in treatment, particularly when we warn our patients to suppress cough as much as possible. By complete rest we put the lungs in as complete circulatory inactivity, relatively speaking, as possible; and we do raise the patient's resistance, but we do this in a mechanical way by striving to avoid any maneuver that will enhance the circulation in the lung and in the tissue around the tubercle.

Consider, too, the accidents that must modify the course that tuberculous infection and disease are going to take. In our struggle to attain definite rationale and generalization in medicine, I sometimes think that we are all too prone to forget the large part that accident plays in the development of a pathological process. A man may have vegetations on his heart valves and these may be continually shed off and lodge in skeletal muscles and no harm result. But another man with an identical cardiac condition may drop dead because the first embolus that breaks loose is swept into his coronary artery. Similarly, accidents undoubtedly determine the course of tuberculosis. It surely makes a great deal of difference whether the first infection in the lungs develops near the pleura or near the hilus or near a large blood vessel or at the apex. The brain is not the only organ of the body that has its silent areas and its eloquent areas. The lungs have theirs too: and the effect will be not so much a matter of resistance as of location. To say that a man who had a caseous gland that erupted into the thoracic duct got generalized miliary tuberculosis because he lacked resistance to tuberculosis, would be just as foolish as to affirm that a man who dropped dead, lacked resistance to coronary embolism.

Besides the accidents of place or location, there are the accidents of time. A great deal may depend on just when a patient develops an intercurrent infection, such as an acute bronchitis, or suffers unsual physical strain. The same episode in his life may produce very different results. It may occur when the concealed tubercle is thoroughly sclerotic and therefore completely withstands the changed anatomical or physiological processes going on in its neighborhood. Or it

may occur at a time when the investing wall of the tubercle has just the proper structure to establish fresh communications with the surrounding tissue under the right conditions. Perhaps this is why young children, if compared with adults, withstand stress and infections relatively poorly so far as the effect of these on quiescent tubercle is concerned. Their tubercle is of comparatively recent origin, is not completely fibrosed or healed and is thus much more open to assault. As they grow older this healing process has advanced further and further, so that we say that in regard to tuberculosis, five to fifteen years is the golden age of man's span. But once having passed puberty they enter a period of from 15 to 20 years when life's stresses are at their maximum and the increased mental and physical strain in many cases produces local effects that are more than even healed tubercle will bear. I say "healed" tubercle with some mental reservation. I would have you recall that living tubercle bacilli have been found in the chalky deposits of tuberculous areas that had healed by calcification. It is for these reasons that I am very fond of telling our students that the development of tuberculous disease from old benign tubercle depends largely on whether the patient gets a cold or rows a race or becomes pregnant at the wrong time.

We have thus far discussed the protective reaction by which the tissues seek to hem in and wall off the first tubercle bacilli that gain entrance to the body and exert their effect upon them. We have also considered local conditions by which the infected organism resists the development of tuberculosis. We have looked upon the tubercle as a growth the periphery of which acts as a barrier to the egress of bacilli and yet is subject to all the physiological disturbance that goes on around it. We have seen how the permanence of benign tubercle or the conversion of benign tubercle into tuberculosis will depend largely on the mechanical interaction and balance of these opposing factors. Let us now extend our line of reasoning to an inquiry into conditions in the patient who presents himself to us with active tuberculosis.

Such a patient, of course, has anatomic change and he has symptoms. Why has he symptoms? Because he is absorbing something from his foci of disease. Why does he absorb something? Because there is a sufficient circulatory give and take between his foci and the surrounding tissue. Why is there this circulatory give and take? Because the walls, the envelopes, the investments of these foci are not competent to block off the interior of the tubercles. If, in course of time, these walls become more and more fibrous and more and more impervious, the severity of the patient's symptoms will surely diminish. This fact is so obvious that I consider it hardly necessary to enlarge upon it. Whether by design or not, we recognize this principle in treating our patients. If they are symptomatic we put them at rest in order to quiet the circulation and respiratory activity. Under such conditions they may be without symptoms. If now we allow them to exercise again symptoms immediately recur. Now their relief from symptoms, their resistance to symptoms, cannot be due to any neutralizing substance which the body elaborates, for, if it is, then we should not expect this prompt response to rest and exercise which by their action on respiration and the circulation we know simply diminish or increase the opportunities for absorption. You have all had patients with incipient tuberculosis who suffered markedly from symptoms of absorption and who, upon the ulceration of their process, informed you that they felt a great deal better. Here by ulceration Nature has applied the prime surgical principle of more or less thorough evacuation of a focus of disease.

The point I want to make is that the presence or absence of symptoms is to a certain extent contingent on focal mechanics. I think we can say absolutely that increasing fibrosis means a gradual release from symptoms; whereas increasing softening without coincident and sufficient peripheral fibrosis means added severity of symptoms. The man who has extensive anatomic tubercle with comparative freedom from symptoms has his tuberculous areas well sclerosed and hemmed in. The man who has but slight anatomic change with marked constitutional disturbances has but very slight investment of his focus. Whether this mechanical element is all that there is to resistance to symptoms I am not prepared to say, but it certainly plays a very large part in resistance.

And, so far as extension of anatomic change is concerned, you can neglect all other factors and assert almost dogmatically that so long as fibrosis is the predominant element in any particular case, just so long are fresh eruptions much less likely to occur than if degeneration and exudation gained the upper hand. Apart from any native or acquired habit of bodily constitution which, in a vague way, we are pleased to call resistance, purely local mechanical conditions play a very large part in resistance to tuberculosis, whether against first infection or against subsequent eruption.

I am, of course, aware that you are all saying, "Yes, but what determines fibrosis and caseation, degeneration and repair? Is it not possible that there is an underlying resistance, a native or acquired attribute of the animal body, that confers upon the tissues the ability to react in such a manner that ideal fibrosis is attained?" Yes, it is not only possible but highly probable; and it is to this phase of resistance that I wish to address myself during the remainder of our inquiry. The manner in which tissues react determines resistance. Let us now examine the probable factors that determine or influence the reactions of tissues. Let us study the reaction of tissues to irritation in general and to the tubercle bacillus in particular.

I take it as axiomatic that individuals vary tremendously in their reaction to irritation. This ability to react in varying degrees is certainly to some extent congenital. Stimulated by the same irritant, one man's cells will over-react while another man's will hardly respond at all. In this connection, Maud Slye's work is of tremendous significance. She works with two large series of mice. The one series consists of animals that have never had cancer bred into them; the other, of those which she is continually fortifying with a cancer heredity by mating their progenitors with individuals of known cancerous stock. She finds that individuals of the

cancer strains react very differently to irritation than do those of clean stocks. If injured, many will develop cancer at the site of the wound whereas none of the non-cancerous strain ever reacts with cancer under the same conditions. Many of the latter, however, become ill with the ordinary infections and die. In cancerous strains, infections are very unusual and, if they occur, are resisted well. She would therefore generalize about as follows: Cancer is the result of a congenital tendency to over-reaction to irritation. Animals with this tendency do not easily acquire infections. If they do develop them, they resist them well. Infections strike down the weak. Cancer attacks the strong.

If Maud Slye's work is sound what shall we say? Shall we conclude that it is possible that the same tissue tendency that is responsible for cancer also protects against infection. Shall we assume that the irritant, the parasitic micro-organism, gains slight foothold or none at all because it is immediately met by an exaggerated effort on the part of the body cells to ward it off? I am here reminded of a remark which that wonderfully keen observer, Dr. Trudeau, repeatedly made—that cancer was a disease of the strong, progressive tuberculosis a disease of the weak. He undoubtedly based this observation on his impression that so many people who developed cancer gave histories that were relatively free from infection during early life. I do not wish to develop this particular phase of the subject further. The point I would ask you to remember is that individuals do vary in their response to irritation, that this response may take the form of an over-reaction, an overgrowth, on over-production of tissue, that evidence is coming in that in some of us this tendency is inbred and that the same mechanism that resists infections may lay us open to cancer if the proper irritation is at work.

If any foreign body that is not assimilable gains access to the body, the tissues react in a characteristic way, that is, with the formation of tubercle. Similarly, tubercle bacilli which are more or less non-assimilable by the tissues, incite the formation of tubercle. Now there are several things that will modify the type of reaction that sets in against the irritant. One is the number of infecting bacilli. Long ago Baumgarten pointed out that, if the bacilli were few, the reaction would be manifested by the proliferation of only one type of cell. If only a few bacilli lodge at a point, then for a number of days the only reaction which we note is a proliferation or renewed growth of those cells which we designate as belonging to the fixed tissue type. The resultant structure is a tubercle that has all the features of a tumor and none of the essentials of an inflammation. Such a tubercle may be made up of cells of the connective tissue type alone. There may not be a leucocyte or any other element of inflammation or exudation in it. Here we have really a growth or new growth or tumor comparable to what under ordinary circumstances we would call a fibroma.

If, however, the initial number of tubercle bacilli is large, the first reaction is an outpouring of polymorphonuclear leucocytes. But within on hour the fixed tissue cells begin to show signs of unrest, and proliferate. The polymorphonuclear leucocytes soon disappear and tubercle formation goes on characteristically with a gradual inwandering of lymphocytic cells which distribute themselves throughout the mass of fixed tissue cells, which in this location have come to be known as epithelioid. We see, therefore, that under ordinary conditions the body reacts to first infection in a variable manner according as the irritation is more or less intense. But the reaction is very regular and definite and, if the infecting bacilli be the first that have gained access to the body, the result will always be the same. The reaction to first infection will always eventuate in the production of *focal* tubercle. The relative proportion of leucocytes and epithelioid cells in different tubercles may vary, but the resultant response to first infection will always be focal. The tubercles will be very definite, isolated and discrete formations, with bacilli near the center and concentric layers of epithelioid cells interspersed with leucocytes forming the periphery. And as we look at them we think of the wall or barrier about which we have said so much. These reactions go on in a perfectly orderly manner. Microscopically, they begin to be evident a few hours after inoculation if ordinary doses of bacilli are used: macroscopically they present themselves to view from about the eighth to the tenth day on. Meanwhile the guinea-pig or rabbit does not exhibit the least symptom of constitutional disturbance from the time the first inoculation is made until the fourth or fifth or sixth week when the disease is progressing rapidly throughout the body.

But note that what I have described applies only to the results of a *first* infection with tubercle bacilli. If I wait until these initial tubercles develop and then reinfect my animals I may get a response of a totally different character. We may watch this response very prettily if we perform our reinfections in the skin (intracutaneously) which we can always keep under observation. We then find that there is an immediate reaction to the reintroduction of tubercle bacilli. Four or five hours after reinfection the tissue at the point of infection begins to inflame. This acute inflammation progresses and after 24 or 48 hours may be marked, both in extent and intensity. It then subsides and a few days later anatomic tubercle begins to develop in the spot. But it develops differently than did the tubercles aroused by the first infection. It appears earlier and has an accelerated development and soon subsides. And unless the reinfecting dose was overwhelming the reinfection may get no further than the skin. In other words, the reaction which we now get is comparable to what we observe when we reinoculate vaccine virus into a person who not long before has had a vaccine "take" or if we reinoculate an animal that has a chancre with a fresh dose of syphilitic virus. The reaction is accelerated and abortive and partakes more of the nature of a pure inflammation, though this latter feature will depend largely on the size of the reinfecting dose.

We are here dealing with a very striking phenomenon, the importance of which is just beginning to be generally recog-

nized. We may pause here for a moment to generalize and say: that the development of anatomic tubercle in the body, consequent upon the introduction of tubercle bacilli, so changes the body that all its tissues react entirely differently from the normal to the application of any soluble protein products of the tubercle bacillus or to the reintroduction of living or dead tubercle bacilli.

Everyone of you has become more or less familiar with this type of reaction in your application of the various cutaneous tests to detect tuberculous infection. And if you have followed the experimental and clinical observations that have been made on this reaction you have learned: 1. That the reaction occurs only when anatomic tubercle is present somewhere in the body. 2. That the reaction begins to manifest itself with the establishment of tubercle. 3. That up to a certain point, as the tuberculous involvement or disease progresses, the intensity of the reaction increases. 4. That as tuberculous disease heals, the intensity of the reaction tends to become less and less. 5. That inasmuch as tubercle is perhaps never entirely eradicated from the body, the power to react is probably never completely lost. These facts are as certain and as easily demonstrable as any that we know concerning tuberculosis. When we formulate them, we are not indulging in the least bit of speculation. And we would state it as a law that the development of tubercle endows the animal body with a capacity to react against the tubercle bacillus or any of its products which it did not possess before. We would go further and state that not only the skin, but all the tissues of the body, the pleura, the peritoneum, the lungs, the liver, etc., take on this changed capacity to react. And we would also recall that no one has yet succeeded in obtaining this changed reactivity in an animal unless he first gave the animal a focus of tuberculous infection.

But with the development of anatomic tubercle other deep-seated changes also take place in the animal body. For 20 years it has been recognized that an animal with tubercle can withstand relatively enormous numbers of living virulent tubercle bacilli as compared with a normal animal. For 20 years and more the details associated with this phenomenon of acquired increased resistance have been studied and the results of these studies may be summarized as follows: 1. The development of anatomic tubercle endows the body with the power to resist greatly increased numbers of tubercle bacilli. 2. This increased resistance to infection manifests itself with the establishment of the first foci. 3. Up to a certain point, resistance is directly proportionate to the extent and severity of the initial disease. 4. With the healing of the diseased foci, resistance diminishes. 5. If the animal remains tuberculous, the increased power to resist is probably never entirely lost, nor does resistance sink to the level which obtained before the animal was first infected. Furthermore, so far as resistance is modified by the introduction of tubercle bacilli or any of its products, this increased resistance can be obtained only by making the animal tuberculous, that is, *by inoculating the animal with tubercle bacilli.* It is true that non-tuberculous animals may be treated with tuberculins of various types and that because of such treatment their serum may contain such bodies as agglutinins, precipitins and opsonins, but such animals are not resistant to infection as compared with normal, non-tuberculous ones. We therefore assume that the ordinary serological antibodies that are met with in tuberculous infection have no direct connection with resistance to infection. In short, when we consider the effects of the tubercle bacillus and any of its products, only the tuberculous animal has a relative immunity to tuberculosis.

For a number of years several of us have been studying this changed reactivity (hypersensitiveness, allergy) and this increased resistance of tuberculous animals. We have never failed to be impressed by the points of contact that the two phenomena exhibit. We have, therefore, wondered whether there was any close or direct relationship between the two. We have thought it reasonable to speculate that perhaps resistance to infection dwelt in this capacity of the tissues of a tuberculous animal to react immediately in an inflammatory manner. It might well be that this initial acute inflammation and the subsequent accelerated development of tubercles took care of the invading bacilli in a more satisfactory manner than did the tissues under ordinary normal conditions. For here the tuberculous animal responds with exaggerated or over-reaction to irritation and throws up a barrier against the bacilli much more actively than normally, and before the bacilli can get under way. From the point of view of the effect of pure inflammation we had some warrant for our belief. Pawlowsky had already demonstrated that if he first inflamed a guinea-pig's knee-joint with a sterile irritant such as turpentine, alcohol or quinine, staphylococci which he then introduced into the joint would not disseminate beyond it, although 24 to 48 hours after the injection of staphylococci into a normal joint, he could recover the micro-organisms from the blood and organs of the guinea-pig. Isayeff had also shown that "the peritonitis induced by a variety of sterile irritants such as a foreign blood serum, bouillon or normal salt solution, temporarily increases resistance to subsequent intraperitoneal inoculations of bacteria." We have therefore done many experiments to validate our view. I regret that to-night I cannot bring to you absolute and definite proof that increased resistance to infection is bound up in and dependent on over-reaction or hypersensitiveness of tissue, but I think that I do not go too far in saying that all the facts point that way.

We can inoculate normal guinea-pigs or rabbits subcutaneously in the groin with a good dose of a more or less virulent strain of tubercle bacilli. After several weeks we find that glandular swellings are developing in the groin and that at the same time the animals' skins are hypersensitive to tuberculin. We can now inoculate such animals intravenously with large quantities of a virulent strain and at the same time inoculate normal animals in a similar manner. The normal

animals do not suffer the least inconvenience or immediate symptom from the inoculation. But within a few hours the reinfected tuberculous animals fall ill and from within 12 hours to four days many of them may die if the dose has been large enough. Those that do not die gradually recover from their acute illness and, as a rule, live on for months and many of them for a year or more, never dying of tuberculosis.

If we section the animals that have fallen acutely ill and have died shortly after reinfection we find that their lungs exhibit areas of hæmorrhagic exudation or acute pneumonia or œdema which we find is the result of tubercle bacilli lodging in already sensitized soil which has over-reacted. Controls sectioned at the same time, up to about eight or ten days after infection, never show these acute pathological reactions. We find, therefore, that animals which we know have increased resistance as well as increased tissue reactivity develop symptoms of illness while they over-react, and we also find that in response to reinfection their tissues react in a particular manner as compared with what occurs after the first infection. The character of the reaction, if the number of organisms at any point is sufficiently large and if the tissues have a very high degree of hypersensitiveness, is exudative or inflammatory, resulting in areas of penumonia or congestion. A first injection of tubercle bacilli, you will remember, never produces such an effect. It excites the body to react only with focal tuberculous change, never with a diffuse process. Remember, however, that I am speaking always of what occurs as the immediate result of the first infection. Remember that a first infection will sensitize an animal after it has progressed for from 10 to 15 days on, and that then any extension of this infection will occur in hypersensitive soil. At any rate, as a result of such experiments we would postulate that the diffuse types of tuberculous lesion, the pneumonias, the pleurisies with effusion, the hydrops of joints, can occur only as the result of reinfection and never upon first infection and that the result of first infection is always a focal, invested tuberculosis. If the reinfecting dose of bacilli is small, then the lesion may also be focal, but the foci develop much more rapidly than upon first infection and they are abortive and tend to disappear.

You see, therefore, that, beginning with a study of resistance to tuberculosis, we are rapidly drifting into the realms of pathology and symptomatology if we pay attention to the wealth of observations that this study of resistance serves up to us. For the first time we can attempt to explain on a solid footing the tremendous variety of lesion that the tubercle bacillus produces in the body, a pathological result that has puzzled and confused observers since autopsies were first performed. As a rule we can affirm that it is the bacillus that is the constant and the animal that is the variable. I can take the same emulsion of the same bacillus and use the same dose to inject a series of animals. If the animals are normal I always obtain the same early result, focal tuberculosis. But if the animals are already tuberculous then almost every variety of lesion is likely to occur and the type of lesion will depend on two factors: on the number of micro-organisms brought to bear at any one point and the degree of hypersensitiveness or over-reaction of the tissue at this point.

Again, we note that symptoms of acute illness occur only in reinfected animals and never in the controls. This suggests what is probably true, that acute tuberculosis never develops as a first infection, that it is acute because it is more of the exudative type and that its exudative type and the acute symptoms are simply expressions of resistance, of over-reaction, of immunity, of hypersensitiveness, call it what you will.

I wish I had time to develop this phase of the inquiry for, as a rule, I find myself growing unaccustomedly eloquent in examining the relationship of resistance to the pathology and symptomatology of tuberculosis. But I have perhaps already taken too much of your time and, like the best writers of fiction, shall close the story by suggestion.

Yet I cannot close without taking this opportunity of making a plea that all who have a lively interest in resistance to tuberculosis, to syphilis and to other infections and to cancer, study these problems from the angle of tissue reactions to irritation. The field is tremendous and has hardly been scratched in a systematic way. We must study the biology of these pathological formations in a developmental manner from the first signs of reaction to irritation right through to ultimate loss of tissue. For many years our pathologists have studied finished tuberculosis as they encountered it at autopsy and only too often have sought to unravel our most difficult problems by meticulous observation of cavity and cheesy patch. But the slender threads that hold the solution to the riddle have long been cut down in the cavity. What we need are careful anatomical and physiological studies of the relation of tubercle to its immediate environment; tubercle of all kinds, tubercle in all stages of development, tubercle as a first infection and tubercle as reinfection, human tubercle in the chicken and avian tubercle in the guinea-pig. What we do not know about tuberculosis almost staggers the imagination when we consider the time that has been spent on its study. How little we really and actually know about what happens after the bacillus has passed the lips and anterior nares! I would therefore appeal for workers in the field. No one man, no school, can discover it all, but if we work together then perhaps we may partially succeed in satisfying that intense longing which all of us have: really to *know* a little corner of our chosen study before we die.

NOTICE.

Owing to the great increase in the cost of all supplies, it has been found necessary to increase the subscription price of THE JOHNS HOPKINS HOSPITAL BULLETIN to $3.00 a year. Single copies will be sold at 50 cents. This increase will take effect at once for all new subscriptions. Renewals will come under the new price as they become due.

THE AMINO-ACID NITROGEN OF THE BLOOD IN CASES OF NORMAL AND COMPLICATED PREGNANCY AND ALSO IN THE NEW-BORN INFANT.

By ARTHUR MORSE.

(From the Department of Obstetrics and Gynecology, Yale Medical School.)

Since the work of Fischer and of Kossel teaches that the protein molecule is composed of amino-acids, we assume that a close analogy exists between the synthesis of polypeptids in the laboratory and the synthesis of protein in the body. Moreover, it is natural to believe that fetal protein is built of amino-acids supplied from the mother's blood. From this standpoint a peculiar interest attaches to the blood of pregnant women, and several fundamental questions arise. We should like to know, for example, whether the maternal blood contains an unusual quantity of amino-acids during pregnancy? How does the quantity of these substances in the mother's blood compare with that in the blood of the fetus? And, in the presence of autointoxications, are abnormal values for the amino-acids encountered in either circulation?

With the Van Slyke method these problems may be profitably studied. However, it is still impossible to estimate the utilization of individual amino-acids by the fetus, as Mendel and Osborne have done in the case of young animals. Not unlikely, what they have found true for the nutrition of lower mammals applies equally to infants, and perhaps also to the preceding period of intrauterine development. But the Van Slyke method, of course, estimates the aliphatic amino-acids only in the aggregate; and others it does not estimate at all. This may not constitute a serious omission and may even prove to be negligible, when the problem is to learn what is the total quantity of amino-acid nitrogen in the blood. But it is noteworthy that some of the amino-acids which Mendel and Osborne have shown to be essential for growth are not included by the Van Slyke method.

Formerly, it was believed that the blood proteins could be satisfactorily removed by precipitation with colloidal iron, before undertaking the estimation of the amino-acid nitrogen; and consequently, in the first cases I studied, the plasma was so treated. For the sake of contrasting that method with the one later adopted, the earlier results are included in this report. But, generally, following the recommendation of Greenwald, a solution of 2.5% trichloracetic acid was used for protein precipitation. With this method higher values are obtained, for the precipitate does not appreciably absorb the amino-acid nitrogen sought in the later analysis of the filtrate. This technique has been adopted by Van Slyke and approved by others, most recently by Bock, who regards the values thus secured as nearly absolute.

The need of a standard with which to compare the values in pregnancy required observations upon normal women. As subjects, we selected patients entering the hospital for the repair of lacerations incident to childbirth, months or years previously, or others requiring a gynecological examination which, however, revealed nothing abnormal. The results indicate that the blood of women contains normally from 8 to 14 mg.[1] of amino-acid nitrogen.

NON-PREGNANT WOMEN.

Number.	Para.	Age.	Amino-acid nitrogen.		Remarks.
			Whole blood per 100 c. c.	Plasma per 100 c. c.	Trichloracetic acid technique.
			mg.	*mg.*	
1	0	18	13.6	12.4	Normal woman.
2	I	26	11.5	8.2	" "
3	I	35	10.6	.....	" "
4	IV	24	9.7	.....	" "
5	V	50	8.6	.....	" "

Because there was not a suitable method for direct determination of the amino-acids in the blood, until recently it was customary to calculate what this fraction of the non-protein nitrogen was. By subtracting the urea-nitrogen from the total non-protein nitrogen, Bang found in a series of 11 women from 6 to 17 mg. of amino-acid nitrogen. An error was involved, since the calculation did not take into account uric acid and creatinin; yet formerly the indirect method yielded more accurate results than direct determinations. For example, after precipitation of the blood-proteins with alcohol the analysis indicates only 5 to 8 mg. as normal; a very low result which, as was said, is explained by the absorptive action of the precipitate.

As normal values, 12 to 13 mg., which come within the range of my determinations, have been recorded by Rosenberg; and the same result was obtained by Gorchkoff, Grigorieff and Koutoursky, who also noted an increase of 3 to 4 mg. after meals.

PREGNANCY.

Number.	Para.	Age.	Amino-acid nitrogen.		Remarks.
			Whole blood per 100 c. c.	Plasma per 100 c. c.	Trichloracetic acid technique.
			mg.	*mg.*	
6	III	30	8.4	7.5	Second month.
7	V	40	8.9	.....	Third month.
8	III	34	9.6	.....	Fifth month.
9	II	28	14.2	.....	Sixth month.
10	I	30	13.6	.....	Eighth month.
11	III	32	10.9	.....	At term.
12	I	30	10.7	8.7	Ninth month. Mitral lesion.

In the blood of pregnant women the amino-acids are not increased; generally, from 8 to 14 mg. are found, the normal

[1] Throughout the paper, the results are expressed in terms of milligrams of amino-acid nitrogen per 100 c. c. of blood, or of plasma, according to the material used for analysis.

range of variations. Among my cases lower values appeared at the 2d and 3d months than later, but this may not be safely ascribed to the period of pregnancy, for quite as large individual differences exist between non-pregnant women. On the other hand, there are several reasons for suspecting consistently lower values in the earlier than in the later months of pregnancy. The former are often characterized by a relatively poor state of nutrition dependent upon loss of appetite, nausea and vomiting, while during the later months usually good health and an excellent state of nutrition are the rule. It is also true that the protein requirements of the embryo are notably less than those of the fetus. Perhaps, then, more extensive material may show a consistent difference between the early and the late months of pregnancy, though from my results it may be said that the values in both periods are within normal limits. Evidently, therefore, the usual quantity of amino-acids in the mother's blood is sufficient for her own needs and for those of the fetus. This finding does not conflict with the demonstration by Wilson and previous observers that a considerable nitrogen-storage takes place during pregnancy, but in conjunction with that fact indicates that the nitrogenous food of the mother is promptly assimilated by the two organisms dependent upon it.

MATERNAL VALUES IN TOXÆMIAS OF PREGNANCY.

Number.	Age and para.	Amino-acid nitrogen.		Remarks
		Whole blood per 100 c. c.	Plasma per 100 c. c.	Trichloracetic acid technique.
		mg.	*mg.*	
13	25	12.6	.....	Pre-eclamptic toxæmia. Hydramnios, 7th month.
	I			B. P. 150, N. P. N. 32.5; Urea N. 19.1 mg.
14	20	15.3	.....	Pre-eclamptic toxæmia. B. P. 170.
	I			Albuminuria 1.4%.
15	20	13.2	.....	Ante-partum eclampsia. B. P. 155.
	I			Albuminuria 6%.
16	24	12.4	5.4	Ante-partum eclampsia. B. P. 180, albuminuria 1.5%.
	I			N. P. N. 47.9; Urea N. 15.9; Uric acid N. 9 mg.
17	38	(a) 17.9	.....	Ante-partum eclampsia. B. P. 200, albuminuria 6%.
	VIII	(b) 17.9	.....	(a) Cæsarean section. (b) 3 days post partum.
18	37	(a) 19.1	.....	Intra-partum eclampsia. B. P. 200, albumin 2%.
	I	(b) 26.1 (c) 28.3	....	(a) Delivery, (b) 8 hours post partum, (c) 30 hours post partum.
19	33	.....	10.3	Post-partum eclampsia.
	III			B. P. 180.
20	37	13.5	.....	Nephritic toxæmia. Fourth month pregnancy.
	II			B. P. 255, albuminuria .4%.
21	37	.....	8.8	Nephritic toxæmia.
	I			B. P. 250, albuminuria 4%.
22	26	.....	7.1	Nephritic toxæmia.
	I			B. P. 190, albuminuria 2.25%.
23	20	15.1	.....	Obscure toxæmia. Pre-eclamptic? No albuminuria.
	I			B. P. 180. Normal delivery. Amino N. of fetus 15.1 mg.
24	20	21.6	.....	Obscure toxæmia. B. P. 155. No albuminuria.
	I			Normal delivery. Amino N. of fetus 21.6 mg.
25	18	21.4	.....	Obscure toxæmia. Diacetic ac. and acetone in urine.
	I			B. P. 110, normal delivery. Amino N. of fetus 24.4 mg. No albuminuria.

When pregnancy was complicated by the presence of an autointoxication, the quantity of amino-acids in the blood was particularly instructive, for the view has long been popular that pre-eclamptic toxæmia and eclampsia are attributable to a derangement of protein metabolism. This view, already discredited by the finding of a normal or slightly increased quantity of non-protein nitrogen in the blood, is also opposed by the fact that the quantity of amino-acid nitrogen present is generally normal. My findings agree with those recently published by Losee and Van Slyke, who failed to demonstrate an increase either in pre-eclamptic toxæmia or in cases in which convulsions were in progress. Occasionally, in my series, values slightly higher than normal were associated with the period of convalescence. Thus, in Case 18 there was a progressive increase in the amino-acid nitrogen during the first and second days after delivery. Recovery also followed in Case 17 which presented the same values on the third day post partum and when the disease was at its height.

While the explanation for the occasional existence of an increased quantity of amino-acids in eclamptics must be purely speculative, it is pertinent to suggest that the dissolution of the corpuscles extravasted in the liver lesion may be responsible. Ordinarily, the destruction of the liver tissue itself is not extensive and would not account for the phenomenon; but at times the hemorrhage into the liver and also into other organs is considerable, so that subsequent autolysis may increase the amino-acids of the blood. If this interpretation is correct, we should expect variable quantities during convalescence from this disease, for the extent of the hemorrhage is by no means the same in all cases. Whatever the cause of the increase in the amino-acid nitrogen occasionally seen during or after eclampsia, it does not depend upon the kidney lesion. At least this view seems justified by the findings in cases of toxæmia referable to renal insufficiency alone; instances of this kind, Cases 20, 21 and 22, present a normal amount of amino-acid nitrogen.

From the viewpoint of autointoxication two cases, in which the clinical diagnosis was obscure, have a peculiar interest, as they present a great increase in the amino-acid nitrogen. An

outline of their histories is given, for they may be helpful toward the recognition of similar cases in the future. It may prove that an increase in the amino-acids of the blood occurs in a specific form of pregnancy-toxæmia.

In these cases the warning symptoms of eclampsia, including headache, visual disturbance, œdema, and albuminuria were absent, and there was no other reason to suspect that the complication was pre-eclamptic toxæmia. On the contrary the high values (21 mg.) for the amino-acids suggest an autolytic process. It is well known that acute yellow atrophy is often associated with pregnancy and also that autolysis of the liver leads to an increase in the amino-acids of the blood. However, jaundice and a lessened area of liver dullness, typical signs of acute yellow atrophy, were absent. In these circumstances the diagnosis was problematical.

No. 24 (S. J. D.) Primipara; 20 years of age; Wassermann negative. Operation scar in appendix region indicates that the wound was infected. No supervision during pregnancy, but patient states her health has been good. Admitted to hospital in labor. Urine negative for albumin and casts. Breech extraction. Female infant with spina bifida. Though it was 50 cm. long the infant's birth-weight was 2600 grams; the mother's menstrual history indicated she was at term. The infant died on the 3d day after birth. The mother's blood pressure was 150 mm. of Hg. at the time of labor and fell gradually to 120 mm. on the 5th day post partum. She was discharged in excellent condition.

No. 25 (D. R.). Primipara; 18 years of age. The patient is poorly nourished and weak; states she has had headache throughout pregnancy and consulted a physician. No jaundice and no disturbance of vision. Vomiting throughout pregnancy. The urine was negative for albumin and casts but contained a large amount of acetone and diacetic acid. Normal blood pressure. Admitted to hospital with symptoms of impending labor but delivery did not occur until 48 hours later. The first stage of labor caused little complaint and the second stage lasted 55 minutes. During one of the pains the patient fainted. Delivery was spontaneous. The female infant was premature, weighing 2000 grams and measuring 45 cm. in length. At the end of two weeks, weighing 1900 grams, it was taken from the hospital against advice. The mother's convalescence was normal and at no time was there arterial hypertension.

MOTHER AND FETUS AT THE TIME OF BIRTH.

At the conclusion of labor the mother's blood contained a normal quantity of amino-acids, and this remained true even though whiffs of chloroform were administered during delivery. In twelve cases of spontaneous birth at full term the extreme values encountered were 8.1 and 13.9 mg. Similar results were obtained during the period of pregnancy and this fact, in conjunction with the demonstration by Slemons and Morriss that there is no difference between the pregnancy- and labor-values for the total non-protein nitrogen and for the urea, indicates that the transition from the one period to the other is not accompanied by alterations in nitrogenous metabolism. The cause of labor, therefore, must be sought elsewhere. The phenomena which accompany labor and direct suspicion toward nitrogenous metabolism as affording the stimulus in question—a low urinary nitrogen, an abnormal relationship between the various nitrogenous excretory products, and mild albuminuria—must be regarded as secondary. These urinary changes, like the more pronounced ones in eclampsia, are the results of an etiological factor still unknown.

NORMAL LABOR.

I PARA.

Number.	Source.	Age of mother.	Duration of labor.	Non-protein nitrogen.	Whole blood.				Plasma.	Remarks.
					Amino-acid nitrogen per 100 c. c.	Urea nitrogen per 100 c. c.	Percentage of amino-acid nitrogen.	Percentage of urea nitrogen.	Amino-acid nitrogen per 100 c. c.	Trichloracetic acid technique.
			hrs.		*mg.*	*mg.*	%	%	*mg.*	
26	Mother.	24	16	....	10.0	....	....	....	7.3	Whiffs of chloroform.
	Fetus..			....	13.1	....	....	....	10.8	Normal infant.
27	Mother.	26	5	26.5	13.9	9.8	52.4	36.9	....	Whiffs of chloroform.
	Fetus..			27.2	15.1	10.7	55.6	39.3	....	Normal infant.
28	Mother.	25	12	33.5	10.5	....	31.4	....	....	Whiffs of chloroform.
	Fetus..			34.2	15.8	....	46.1	....	....	Normal infant.
29	Mother.	21	8¼	....	8.1	....	....	....	....	Whiffs of chloroform.
	Fetus..			....	10.6	....	....	....	....	Normal infant.

III PARA.

30	Mother.	33	8	....	10.8	....	....	....	6.7	No anæsthesia.
	Fetus..			....	10.0	....	....	....	9.2	Normal infant.
31	Mother.	20	13¾	....	10.1	....	....	....	8.1	Whiffs of chloroform.
	Fetus..			....	12.9	....	....	....	11.4	Normal infant.
32	Mother.	22	22	....	10.0	....	....	....	....	Whiffs of chloroform.
	Fetus..			....	15.7	....	....	....	....	Normal infant.

IV PARA.

33	Mother.	36	14	27.7	13.7	13.1	49.4	47.2	....	Whiffs of chloroform
	Fetus..			27.1	14.8	13.5	54.6	49.8	....	Normal infant.
34	Mother.	34	4	26.5	11.4	11.6	43.0	44.0	....	Whiffs of chloroform.
	Fetus..			27.5	12.9	10.0	46.9	36.6	....	Normal infant.
35	Mother.	25	26	....	11.2	....	....	....	....	Whiffs of chloroform.
	Fetus..			....	12.7	....	....	....	....	Normal infant.

V PARA.

36	Mother.	23	4½	....	10.9	....	....	....	10.0	No anæsthesia.
	Fetus..			....	14.9	....	....	....	11.1	Normal infant.
37	Mother.	23	12½	....	12.8	....	....	....	....	Whiffs of chloroform.
	Fetus..			....	11.3	....	....	....	....	Normal infant.

OBSTETRICAL OPERATIONS.

38	Mother.	27	15¾	....	10.7	....	....	....	6.6	Forceps. Chloroform.
	Fetus..	I		....	13.2	....	....	....	9.1	Normal infant.
39	Mother.	18	21½	....	9.0	....	....	....	8.2	Forceps. Chloroform.
	Fetus..	I		....	13.4	....	....	....	11.6	Normal infant.
40	Mother.	30	....	....	11.0	....	....	....	....	Forceps. Chloroform.
	Fetus..	I		....	10.4	....	....	....	....	Slight asphyxia.
41	Mother.	30	16	....	10.8	....	....	....	....	Forceps. Chloroform.
	Fetus..	VII		....	15.0	....	....	....	....	Normal infant.
42	Mother.	35	....	....	11.7	....	....	....	....	Version. Chloroform.
	Fetus..	VII		....	12.8	....	....	....	....	Normal infant.
43	Mother.	30	....	....	13.0	....	....	....	....	Cæsarean. Nitr's ox.
	Fetus..	I		....	13.0	....	....	....	....	Normal infant.

When delivery has been effected by an operative procedure under deep anæsthesia normal values for the amino-acid nitrogen of the blood are found. Thus, in five cases requiring the surgical degree of chloroform anæsthesia, the average amino-

acid nitrogen was 10.6 mg.; in ten cases given a few whiffs of chloroform it was 11.1 mg., and in two delivered without an anæsthetic 10.8 mg. The similarity of these results indicates that chloroform anæsthesia does not affect the amino-acids of the blood; and in this respect it resembles ether, the effects of which have been studied by Ross.

As an interest in the placental interchange was one incentive to undertake these observations, both "whole blood" and plasma were analysed independently. In maternal blood the amino-acid nitrogen of the plasma varied from 6.6 mg. to 10 mg. Obviously, these values are much lower than those found when "whole blood" was analysed (8 to 14 mg.), and indicate that the red blood corpuscles per unit of volume contain a relatively larger quantity of amino-acids than does plasma—a fact previously established by Costatino, Bang, and Gyorgy and Zunz.

To explain the presence of these substances in the red blood cells two hypotheses have been offered, namely: (1) that the union is temporary and provides facilities for the transportation of amino-acids from one part of the body to another; and (2) that the cells are broken down ultimately by an intracellular enzyme which liberates amino-acids. In the latter event, the food value of these autolytic products has been questioned; but as far as we know, the body is incapable of distinguishing between amino-acids absorbed from the digestive tract and others arising from its own tissues. And besides, it is improbable that hæmolysis normally is a factor of appreciable importance in this problem. The weight of evidence at present is in favor of the first hypothesis.

The fetal blood used for analysis was obtained from the placental end of the severed umbilical cord. It has already been shown by Slemons and Morriss that such specimens are derived from the umbilical vein and, therefore, are arterial, having just left the fetal side of the placenta.

In 18 normal infants the amino-acid nitrogen of the blood at birth varied between 10 and 15.8 mg. As in the case of adults, higher values are obtained for "whole blood" than for plasma; in the latter there was from 9.1 to 11.6 mg. Very much lower results were obtained by Morel and Mouriquand who used alcohol to remove the blood proteins. Similarly, when colloidal iron was the precipitant, as in the first series of analyses I made, the results were far too low because the precipitate absorbed a portion of the amino-acid nitrogen.

Not many years ago it seemed that the fetus must derive its nitrogenous food from the proteins of the mother's blood, for at that time it was thought that the elementary substances out of which protein is built were not present in maternal blood. But with the demonstration that amino-acids are normal constituents of human blood (Folin, Delaunay, Van Slyke and Meyer) it seemed reasonable to assume that the mother supplied the "building stones" themselves, for the construction of fetal protein. This explanation was the more likely because amino-acids are crystalline, and many of them, at least, are diffusible compounds. By means of ingeniously contrived collodion tubes, immersed in salt solution, Abel succeeded in showing that amino-acids were among the substances which dialysed out of blood. Later, Abderhalden identified many amino-acids which had passed from blood through a permeable membrane. Upon these grounds it was reasonable to expect that these compounds passed through the placenta and, now that approximately the same quantities of them are demonstrable in maternal and fetal blood, the correctness of the assumption is scarcely open to doubt. The mechanism of exchange, however, would not seem to be one of simple diffusion.

When samples of "whole blood" are analysed, generally, the fetal sample contains somewhat more amino-acid nitrogen than the maternal sample. In 18 cases identical results were obtained in four instances; the mother's blood was the

MATERNAL AND FETAL PLASMA.

(When colloidal iron was used for preliminary precipitation of the blood proteins.)

Number.	Source.	Age and para.	Duration of labor.	Amino-acid nitrogen per 100 c. c.	Remarks.
			hrs.	*mg.*	
44	Mother.	22	52¾	5.3	Normal labor. No anæsthesia.
	Fetus..	I		7.0	Normal infant.
45	Mother.	33	4	5.9	Normal labor. No anæsthesia.
	Fetus..	II		7.9	Normal infant.
46	Mother.	25	9	5.3	Normal labor. No anæsthesia.
	Fetus..	III		7.8	Normal infant.
47	Mother.	29	14½	6.5	Normal labor. No anæsthesia.
	Fetus..	IV		8.2	Normal infant.
48	Mother.	34	2¼	7.2	Normal labor. No anæsthesia.
	Fetus..	V		11.9	Premature infant (eighth month).
49	Mother.	31	27½	5.6	Normal labor. Whiffs of chloroform.
	Fetus..	I		7.6	Normal infant.
50	Mother.	28	9¼	6.6	Normal labor. Whiffs of chloroform.
	Fetus..	II		8.3	Normal infant.
51	Mother.	21	4¼	4.9	Normal labor. Whiffs of chloroform.
	Fetus..	II		6.8	Normal infant.
52	Mother.	20	10¼	5.0	Normal labor. Morphine and tyramine.
	Fetus..	I		6.4	Normal infant.
53	Mother.	20	19¾	5.6	Normal labor. Morphine and tyramine.
	Fetus..	I		7.3	Normal infant.
54	Mother.	22	105½	4.5	Low forceps. Deep chloroform.
	Fetus..			6.2	Normal infant.

richer in one instance, and the fetal blood the richer in 13. The higher red cell count of the fetus, it was believed, might be responsible for the slight preponderance of amino-acids in that organism, especially since Costatino showed that the nucleated red cells of birds contain more amino-acids than the unnucleated red cells of mammals, and nucleated red cells are present in the fetus at the time of birth. However, the possible influence of that factor was eliminated by the finding that fetal plasma is richer in amino-acids than maternal plasma, and also by finding that the difference between the two plasmas closely resembled the difference when "whole blood" was analysed, namely about 2 mg. per 100 c. c. But to some extent, it must be said, that an unsurmounted difficulty modifies this evidence. Fetal red corpuscles are extremely fragile, and with a few exceptions slight hemolysis was observed after centrifugalization. Nevertheless, the error thus caused may

be regarded as small, though obviously it exaggerates the difference between the maternal and fetal specimens of blood.

In the face of higher fetal values (in approximately 70% of the cases) small as the difference is, mere diffusion cannot be said to explain the passage of amino-acids through the placenta. This problem presents much in common with the problem arising when large amounts of amino-acids are injected into the circulation of an animal. Experimentally, Van Slyke has found that amino-acids pass rapidly into the tissues, and are loosely held there, probably by physical rather than chemical means. An equilibrium is reached when the tissues contain about ten times as much amino-acid nitrogen as the blood does. "The process concerned in the exchange has not been definitely classified and at present we cover our ignorance of its real nature by giving it the general name, *absorption*" (Van Slyke).

Although the equilibrium between maternal and fetal blood is reached when the concentration of amino-acids in the two circulations is more nearly equal than in the case of the blood and tissues in the experiments just quoted, it seems that the placenta like other tissues must possess this same quality of "absorption." On the other hand, the close resemblance between maternal and fetal concentrations is highly significant, indicating an extremely delicate regulatory mechanism for equalizing the amino-acid content of the two circulations per unit of blood volume. The results of this regulation are illustrated by the findings in cases of hyperaminemia (Nos. 24 and 25); in the former identical values (21.6 mg.) were obtained in both organisms, while in the latter 21.4 mg. were found in the maternal and 24.4 mg. in the fetal blood.

The existence of a slightly higher fetal than maternal amino-acid nitrogen in most cases not only suggests the ability of the placenta "to absorb" these substances, but the purpose of this mechanism may be interpreted as protective. When the maternal values are very high, the fetal values duplicate or exceed those in the parent. On the other hand, high fetal values may be associated with normal maternal ones (Cases 28, 32, 41). It seems probable, therefore, that once amino-acids have entered the fetus, it may not be deprived of them, and this provision in a measure insures a supply of material out of which fetal protein is built.

CONCLUSIONS.

1. In normal women the amino-acid nitrogen varied between 8 and 14 mg. per 100 c. c. of blood; and the same range of variations was encountered during pregnancy. In other words, the requirements of the fetus cause no increase of the substances in the maternal blood out of which protein is constructed.

2. Generally, normal values were found in pre-eclamptic toxæmia and eclampsia, though exceptionally an increase in the amino-acids occurred during convalescence.

3. Nephritic toxæmia was accompanied by a normal quantity of amino-acid nitrogen in the blood.

4. An excessive quantity of amino-acids occurred in cases of obscure toxæmia, possibly related to acute yellow atrophy of the liver.

5. During labor normal values were found; at its conclusion the extremes encountered were 8.1 and 13.9 mg.

6. In fetal blood the amino-acid nitrogen varied between 10 and 15.8 mg. per 100 c. c. of blood.

7. The passage of amino-acids from mother to fetus requires the assumption of "absorption" properties on the part of the placenta; for, though the difference between the concentration of amino-acids in the two circulations is small, it is in favor of the fetus in 70% of the cases; and the higher level in that organism prevents the acceptance of simple diffusion as the explanation for the placental exchange.

8. The "absorption" property of the placenta probably protects the fetus against loss of material intended for the construction of protein.

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ON THE ETYMOLOGY, POPULAR AND SCIENTIFIC, OF THE TERMS FOR KIDNEY, IN VARIOUS LANGUAGES.*†

By David I. Macht, A. B., LL. B., M. D., F. S. J. A.

Introductory.

The subject of this paper may, on first thought, appear to be more suitable for presentation before a philological rather than a medical assembly. A moment's reflection, however, I venture to say, will suffice to convince that it very appropriately falls within the scope of such a society as this one. The field of interest of medical history is so far-reaching that it overlaps the domains of anthropology, ethnology, and every other branch of biology, among which we certainly must class comparative philology, or the study of the development of speech and its means of communication, or language. An inquiry into the history of some of the simplest terms used in medicine may result in a valuable contribution to the history of the anatomical, physiological, or psychological conceptions of a race or people. That such an inquiry is an interesting discipline, I think, goes without saying. An additional fascination, moreover, attaches itself to it, because for its purposes we are not confined to the limits laid down by what is known as scientific etymology or philology, but may also legitimately draw upon the rich store-house of information classed as folk-lore and popular etymology.

In the present essay, I have endeavored to trace the history of the words for kidney in a number of languages. Such an inquiry was deemed of especial interest because the kidneys have in the last few years been the subject of particular attention and intensive study in this hospital, and because of a number of important discoveries in connection with them which have emanated from this medical school. I am referring in particular to the pioneer work on epinephrin by Prof. Abel[1]; to the invention also by him of the process of vividiffusion by means of what has come to be known as an "artificial kidney," of which we have a model here[2]; and to the introduction of the phenol-sulphone-phthalein test for renal function, also started by Prof. Abel and elaborated by Drs. Rowntree and Gerahty.[3] I was further prompted to undertake an investigation of the subject through my keen interest in Semitic philology and Biblical psychology.

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The English "Kidneys" and "Reins."[4]

The two English names "Kidneys" and "Reins" illustrate well the composite character of our language, for they take us back to the two most important roots for that organ in the Indo-European languages.

The word "Kidney" consists of two elements "kid" and "ney"; the first of which, according to Professor Bright, must be pronounced unidentified, while the second is probably the same as the German *Niere*. The Middle English form *Kid-nere*, and the Icelandic and old Norse *nyra*, make this relation pretty certain. In Middle English, however, other forms besides kidnere—as for instance, *kid-neer*—led to a confusion of the second element of the word kid-ney, with *ey* or *eye*, corresponding to the German *Eier*, or testicles. This confusion of the kidneys with testicles, as will be seen later, is met with in many languages.

Although the etymology of the first element *kid* of kidney is uncertain, it has been thought to represent the Anglo-Saxon *cwiδ* or *cwith*, the Scandinavian *kviδr* and the Gothic *quithus*, all of which signify stomach or belly. In such a case the meaning of the word kidney would be the *Niere* or the *Eier* of the abdomen, a kind of abdominal tumor. This etymology is, however, not considered correct.

Our other terms for kidneys—*reins*, is readily recognized as the Old French *reins*, which in its turn is derived from the Latin *ren* (pl. *renes*). It is this term in English which is chiefly employed figuratively in the sense of "inward parts, temperament, inner affections or passions." The origin of this expression we shall consider in connection with the Hebrew term for kidney.

The Latin "Ren" and Its Derivatives.

The Latin *ren* (pl. *renes*) is the prototype for the word for kidneys in all the modern Romance languages, and also, as has been just mentioned, of the English *reins*. From it have come the French *reins*, the Italian *rene*, and the Portuguese *rim*; and from its descendant, the late Latin *reniones*, we get the French *rognons* (used of animals only) and the Spanish *riñon*.

The derivation of the word *ren*, according to Prof. K. F. Smith, is altogether uncertain. The old medical writers, however, have some curious notions concerning it. Thus Matthew Timlingio cites Varro as calling *renes* a synonym of *rivuli*,

meaning channels, ducts, or streams. Another curious hypothesis regards *ren* as coming through a metathesis of *n* and *r* from the Greek *νηρόν*, wet or humid. Still other writers consider *ren* to be derived from the Greek *Φρήν* (*diaphragm, mind*), from the supposed relation between the kidneys and the mind, but this explanation is obviously a late attempt of the medieval scholars to find a physical basis for their philosophy.

We have another old Latin word for kidneys, namely *nefrones*. This is clearly a transliteration of the Greek *νεφρός*, which we are now going to consider.

THE GREEK "NEPHROS" AND THE GERMAN "NIERE."

Just as the Latin *renes* is the predecessor of the names for kidney in the Romance languages, and of the English *reins*, so is the Greek *νεφρός*, met with so frequently in our present medical nomenclature (*e. g.*, nephritis, nephrolithiasis, epinephrin, etc.), the precursor of the German Niere and other Germanic forms, and also probably of the second element of our English kid-ney. The relation of *Niere* to *νεφρός* is a very interesting one, and is a good example of the methods employed and results achieved by the modern scientific comparative philologists. Both *νεφρός* and Niere come from an original Indo-European posited or hypothetical root "neg^{u}hros." The g^{u}h of this root, by a well attested relation, appears as *φ*(ph) in Greek, and thus gives *νεφρός*, from which are derived the Praenestine *nefrones*, and the Lanuvian *nebrundines*. In the Pregermanic or Gothic forms the g^{u}h of the primitive root is softened into an *i*, giving rise to the Gothic *nioro*, the old Norse and Icelandic *nyra*, the old Swedish *niure*, and the modern German *Niere*. (Curtius[5] 316. Osthoff 1F. N 271 sq. bibl. Brugmann Grdr. I^{2}588, 613, 634, II^{2}, 1, 289, 354, 607, Walde. 1F. XIX, 102.)

That the linguistic relation between the Greek *νεφρός* and the German *Niere* here described is probably a correct one is further substantiated by the fact that both the Greek *νεφρός* and the Old High German *nioro* (masc.) are used in a twofold sense—sometimes for kidney, and in other cases for *testicle*. Eustathius, for instance, in his Commentary on the Iliad Φ 204 (=p. 1231 ed. Bas.), states this distinctly.

ἔστι δὲ ἐπινεφρίδιος δημὸς ὁ ἐπὶ τοῖς νεφροῖς τοῖς κυρίως, προσεθέμεθα δὲ τὸ κυρίως πρὸς διαστολὴν τῶν μὴ τοιούτων, δοκοῦσι γὰρ ἀστείως καὶ οἱ ὄρχει νεφροὶ κληθῆναι παρὰ τῷ εἰπόντι τό.

This confusion of the kidneys with the testes is found also in other languages. Thus the Old Latin *nebrundines* is used for both *reins*, and *testes;* the Italian *rene*, kidney, means also testicle; and some linguists suspect that the Old English phrase "a man of some kidney," where the specific idea expressed by the word comes close to that of virility, might be a survival of the ancient signification of the Greek *νεφρός* and Gothic *nioro*.

The Latin *nebrundines*, it may be well to note, is still preserved in the vulgar German *brunzen*, to micturate.[6]

The comparative philologists have not only succeeded in tracing Niere back to *νεφρός*, but have also endeavored to correlate *νεφρός* with the Latin *ren*. The process here is a rather intricate one and not very clear, but is of especial interest to the medical student. The Greek word *ἀδήν* (*ἀδένος*), meaning gland or tumor, which we find in our medical terms adenitis, adenoids, adenoma, etc., comes from a primitive form ng^{u}en. From this primitive root or form are derived also the Latin *inguen*, groin, French *aine*, and Old Norse *økkuen*, meaning tumor or swelling. The form ng^{u}en is furthermore correlated by comparative philologists on the one hand with the primitive neg^{u}hron and on the other hand with the Old Irish *āru* (pl. ārain), and Gallic *āren*, kidney, which closely resemble the Latin *ren*. It is thus suggested that both the Greek *νεφρός* and Latin *ren* are distantly related to the word *ἀδήν*, which means a tumor or swelling. (Saussure MSL VI, 53, Brugmann Grdr. I^{2} 391, 408, 593, 634. KV. G. 128, Hirt. Abl. §633. Bezzenberger 33, 27, 141.)

The old medical writers were not so well versed in linguistic and phonetic laws, and endeavored to explain the word *νεφρός* on the basis of popular etymology, which meant very often an attempt to correlate the meaning of the word root with their conception of the organ. Though this is not strictly speaking philology, such explanations are of considerable medico-historical interest. Thus, M. Tilingius in 1709, in his Dissertation entitled Nephrologia Nova et Curiosa,[7] regards the word *νεφρός* as consisting of two elements, *νεφ-* and *-ρος*, the first of which is related to the word *νέφος*, cloud or mist (*cf.* our word nephelometer), whence the verb *νείφειν*, to snow or rain, whereas the second is related to the word *ῥεῖν*, to flow (*cf.* diarrhœa, leucorrhœa, gonorrhœa, etc.). The idea suggested is therefore the curious "pneumatistic" conception of the old philosophers, who regarded various spirits or vapors as being condensed in the body and eliminated by the kidneys.[8]

SLAVIC NOMENCLATURE.

Turning our attention from the classical and West European to the East European or Slavic tongues, we meet with a variety of words for kidney, some of which are already familiar, while others are new and peculiar.

The Polish *nyrka* and Bohemian *nerka* are plainly identical with the German *Niere*. Another word for kidney in Polish is *cynadry*. This Prof. Wiener correlates with the German *Geschnader*, and means literally entrails.

Another term commonly designating kidneys in Bohemian is *ledwina* or *ledwinka*. Similarly in Slavonian we find *ledvica*. These three words are all derivatives of the old High German *lenti*, modern German *Lenden*, or loins.

The Russian word for kidney is entirely different from those in other Slavic languages. It is *počka* (pronounced pot-chka) and means a *bud*. The underlying idea is not certain. According to some the word bud is used here in the sense of small swelling, and has reference to the shape of the kidney. According to others, the underlying idea may be that of germination and procreation.

The Lithuanian word for kidney is *inskstas*, which means also any hard swelling. The cognate Lettish words for kidney,

inksts, and for the thumb, *inkschkis*. Prof. Prince is inclined to think also express the same idea of tumor or swelling.

In Serbian and Bulgarian the common word for kidney is *bubreg*. This, according to Prof. Prince, is properly from the Turkish *brughrek*, "kidney," and really means something *rounded off*; an idea akin to the swelling concept.

Sanskrit.

The Sanskrit tongue which so frequently furnishes the comparative philologist with valuable information, can, according to Prof. Bloomfield, throw very little light on the etymology of the word for kidney in other Indo-European tongues. The Sanskrit word is the *dual vṛkkau*, and is related to the old Persian *veredka*. An ultimate analysis of the word is not possible.

Analysis of the Indo-European Terminology.

Before proceeding to the consideration of some Oriental languages, it may be well to compare the various words for kidneys already studied. It will be noted *firstly* that the meaning of most of the names examined refers to the rotundity or shape of the organ. Thus, both the Greek **νεφρός** and Latin *ren* (which are the forebears of the Romance and Germanic terms) are related to the word **ἀδήν**, and express the idea of tumor or swelling. The Russian *počka*, bud (German, *Knospe*), is also a rounded protuberance or mass. The Lithuanian and Lettish *insktas* express the same idea; and the Bulgarian and Serbian *bubreg* again imply a something rounded off.

Secondly, it is interesting to note the application of the same terms to both the kidneys and the testes. This confusion was obviously due to the close anatomical relationship of the genital and urinary organs, and to the fact that the testes are in many animals to be found situated in the abdominal cavity. Etymologically, of course, the word for kidney, meaning merely a rounded mass or tumor, could be well applied to either testicles or reins.

Thirdly, as a result of this double signification of words, the term kidney came to be employed figuratively to convey the idea of virility or strength. The classical **νεφρός** and the Gothic *nioro* were frequently used in that sense, and as already mentioned, a survival of this ancient usage is probably preserved in our English phrase, "a man of kidney"; or in the expression, "He has no kidney," meaning, "He is a poor specimen of manhood." Compare, again, this passage from George Eliot (Daniel Deronda, Vol. II, Ch. 60, p. 334: "There have always been enough of his kidneys, whose piety lies in punishing." Another striking example of this conception is found in old Slavonian, in which the word for kidney is *Mozek*—the literal meaning of which is "little man." In the female a similar relation, it seems, was assumed to exist between the kidneys and the *testes muliebres*, or female testes, *i. e.*, the ovaries.

Lastly, it is well to call attention to the fact that the confusion between the testes and the kidneys was not only from the anatomical point of view, but also in regard to their physiological function. Preparation or elaboration of the semen was considered to be one of the functions of the kidney in man, and we find this doctrine in medical works as late as the 18th century. Bartholin in his Anatomia (Leyden, 1673) cites Olhafius, Sennertus, Wormius, Hofmann, Meibomius, Horstius, Loselius, Eichardius, Sperlinger and others as holding that view, and he himself proceeds then to reconcile it with the phenomena of circulation, recently advanced at that time by Harvey. Horstius (Opera Medica, 1661, p. 646) says: "Renum triplex statuitur actio et usus. Primus statuitur in promovendo actu naturalis seminationis." (Of the three uses of the kidneys, the first is in promoting the action of semen.)

Again, in the venerable treatise on kidneys by Tiling (1709), we read:

"Renum usum nobilem non in expurgando solum a sanguine seroso et salso excremento, sed in coequendo et perficiendo quoque sanguine, itemque potissimum in seminis preparatione ac ejusdem fecundatione consistere." "The noble use of the kidneys is not alone for elimination from the blood of serous excrement and salt, but also in elaborating and perfecting semen and fecundating it." Johan P. Hollardus, in another dissertation, *De Renum Structura et Usu* (Basel, 1705), actually declares that the size of the kidneys is an index of sexual power.

The Russian word for kidney—which means "bud"—seems also to convey this idea. Even Thomas Gibson, in his English "Anatomy of Humane Bodies," London, 1703, p. 131, writes the following: "Some have thought that the kidneys besides the separating of the Serum prepare matter for the seed..... This opinion is exploded by the circulation of the blood. Yet, however, though they do not prepare matter for seed, yet by separating the salts and other recrements, they amend the disposition of the blood so that it becomes more capable of being elaborated into seed by the vasa preparantia and testes."

Chinese and Japanese.[m]

Passing to the Oriental languages, we find that the curious and fanciful conceptions just described appear in a more poetical and picturesque garb in Chinese and Japanese, the words for kidney being identical in the two languages. I have received some very interesting information on the subject from Dr. Yates Wang, of the Chinese Legation at Washington. The name *shen tsang* in Chinese (Japanese *zin-zo*), signifies both kidneys and testicles. The Chinese medical philosophers, however, differentiated the functions of the two kidneys. The left one was known as the internal kidney, and had to do with the secretion of urine. The right kidney, on the other hand, was called the gate of life, and was thought to secrete or elaborate semen and to pass it on to the external kidney or testicles.

An ultimate analysis of the word *shen tsang* gives us still more interesting information. The first syllable, *shen*, consists of two elements, the upper one meaning *wisdom*, and the lower meaning *flesh*. The second syllable, *tsang*, means an internal organ for storage of water. The picture language thus conveys

the idea that the kidneys are secreting organs on the one hand, and the seats of wisdom on the other. This conception is peculiarly Oriental, and probably originated from the idea that Wisdom dwells in the innermost recesses and deepest lying organs of the body, such as the kidneys are.

POLYNESIAN AND MALAY.

I have not been able to secure much information concerning the words for kidney and testicles in these languages. Dr. F. R. Blake tells me that the Taglog for kidney is *bato nang kata, wan*, and means "stone of the body," referring as in the European languages to its shape; whereas testicles is *itlog* or ovulum. In Bisaya, the same word is used. In Sulee the word for testicle in *bigi buyang*, bigi meaning *seed*.

SEMITIC TERMINOLOGY.

I have purposely reserved the consideration of the Semitic words for kidney for the last, on account of the special interest attaching to them intrinsically, and because of the influence exerted by the Hebrew conception of the kidneys, through the medium of the Bible, upon the use of the word "reins" in English and other modern languages.

The name for kidney is the same in all Semitic languages, with the exception of Sumerian. In Sumerian that organ is called *bir*, which, according to Prof. Haupt, means to tear, lacerate, make incisions, and may have a reference to its indented form. In Hebrew the word for kidney is *kilia;* in Assyrian, *kalîtu;* in Arabic, *Kuliatun;* in Syriac, *Kulita;* in Coptic, *Gloole*, and in Aramaic, *kulia*.[21] As all these words come from the same root *Kl*, which means to hold or contain, we shall confine ourselves to an analysis of the Hebrew *kilia*.

THE BIBLICAL KELAYOTH.

The Hebrew *kilia* (pl. kelayoth), according to Gesenius and most other authorities,[22] comes from the same root (Kl), and is really a variant form of the Hebrew word *keli*, a vessel. This being the case, a very curious coincidence immediately suggests itself to the medical man.

In most of the important languages that we may examine, the word for vessel (container, or receptacle), is either alone or with a qualifying adjective "blood," employed to designate *blood-vessels*. Thus we have the English *vessel*, the German *Gefäss*, the French *vaisseau*, the Russian *sosud*, the Latin *vasum*, the Greek ἄγγος, and others, all used in both senses. Now, although we find no Hebrew word for blood-vessels in classical (Biblical) literature, in modern Hebrew the expression keli dam, "vessel of blood," may quite legitimately be employed in such a sense. The Biblical word for kidneys may therefore be taken literally to signify vessels, or blood-vessels. That, however, is essentially the modern conception of the kidneys—a vascular organ, a "bunch of blood-vessels" or glomeruli, so to say, for the elimination of waste products from the blood. A glance at Prof. Abel's so-called "artificial kidney," which we have exhibited here, and which consists simply of a large number of artificial collodion dialyzing tubes or "blood-vessels," will make the conception more clear. I am mentioning this curious coincidence, not as an example of scientific philological reasoning, but as an admirable example of how ancient conceptions may sometimes harmonize with modern thought. Moreover, after all such a teleological interpretation of the Biblical *Kilia* is no more forced than the derivation of the Greek νεφρός from ἀδήν, for it is very questionable whether νεφρός would have ever been traced to ἀδήν, had not the philologists first perceived a similarity in shape between kidney and gland.

It is well to note that the common confusion of kidneys with the testicles and the ambiguous use of the same word to express both so often met by us in the other languages is not found in the Bible. Here we have a distinct term *eshek* (Leviticus XXI, 20) for the latter organ, and in the Talmud the word *bezim* (eggs) are used in the same sense. It is only in Aramaic that the term *kulia* is met with in both senses, and that may possibly be due to foreign influence.[23]

This careful anatomical distinction between the genital (testes and ovaries) and urinary organs (kidneys) met with in the Hebrew literature is undoubtedly due, to some extent at least, to the explicit laws and directions pertaining to the sacrifices. These rites necessitated careful dissection of the animals, and the separation of various organs, among which the kidneys *"and the fat that is upon them"* occupied an important place.

Though anatomically distinct, the kidneys, however, were correlated with the sexual sphere in a psychological sense. While the head, in Biblical figures of speech, is mentioned as the seat of *thought*,[24] as for instance in Daniel II, 28, IV, 27, etc., the seat of the *will*, and of all higher, nobler and ethical emotions is referred to the heart, "for from it are the issues of life." (Prov. IV, 23.) The kidneys, on the other hand, were believed to be connected with the lower, animal passions, or as some writers describe it, with the *vegetative sphere*.

"Und scheinen somit *kilioth* für das Reich vegetativer Reize und Antriebe dieselbe Stellung inne zu haben, wie das Herz für das Gebiet der höheren Empfindungen und Bestrebungen." (S. R. Hirsch, on Lev. III, 4.)

This figurative use of the word kidneys has passed from the Bible to the modern languages. Thus the meaning of *reins* is given by our dictionaries, besides its primary signification of kidneys, as *temperament, affections, passions*.

Here again the medical man cannot fail to note an interesting coincidence. The relation of the reins to the major emotions, in the light of recent physiological psychology is not merely a metaphoric one. All who are acquainted with the fascinating researches of Cannon and his school on the rôle played by epinephrin in emotive states,[25] will not fail to appreciate the aptness of the Biblical expression—reins, which we must remember always means the *kidneys and the fat that is on them, i. e.*, includes the adrenals.

So important was this function considered, that some writers liked to trace a relation between the word *kilia*, kidney, and the root *Kalah*, to long for, to desire passionately.

The Hebrew word *tu-ach*, meaning something covered over, hence, inward parts (Ps. LI, 8; Job XXXVIII, 36) (Vulgate "in visceribus"), has been rendered by some commentators as reins. This interpretation, in connection with the verse in Job "who puts wisdom in the inward parts," led to the erroneous view akin to the Chinese conception, that the kidneys were intimately connected with the seat of wisdom. There is no philological or other basis for this assumption. Wherever the reins are spoken of figuratively as correcting or admonishing, it is always in the ethical sense mentioned above, namely, as controlling our animal or grosser passions. (*Cf.* Talmud, Berakoth 61, a.)

Finally, I wish to call attention to another interesting coincidence between the Biblical usage of the term reins, and our medical conceptions and associations, and that is the remarkable juxtaposition of the terms heart and kidneys. Out of some 13 passages in which the kidneys are spoken of figuratively in the Old Testament, the word is employed no less than 6 times in apposition to the heart. We find the expressions, "probing heart and reins" (Jer. XI, 20; Ps. VII, 10), "searching heart and reins" (Jer. XVII, 10), "seeing heart and reins" (Jer. XX, 12), "cleansing heart and reins" (Ps. VI, 2). In each case the idea intended to be conveyed is the interdependence of the higher and lower emotions as symbolized by the heart and reins. Just note the literal translation of the Hebrew Ps. LXXIII, 21, "When my heart is oppressed, then am I smitten in my reins." How fitting the simile in these days of cardiopathies and nephropathies, when the two are found to be so closely related as to be impossible of sharp differentiation!

So, as we close, we cannot help but think that the figures of speech and metaphors of the good old Book are up to date, and may be appreciated now as much as in the days of yore—if not, perhaps, a little more!

In conclusion, I take great pleasure in acknowledging with thanks valuable suggestions received from Dr. F. R. Blake, Prof. Paul Haupt, Prof. M. Bloomfield, Prof. J. Bright, Prof. F. K. Smith, Prof. C. W. E. Miller, and Prof. Henry Wood, of this University; from Prof. L. Wiener of Harvard and Prof. J. D. Prince of Columbia; Librarian-in-Chief H. Putnam and Dr. Israel Shapiro, of the Congressional Library; Dr. F. H. Garrison, of the Surgeon-General's Library, and Dr. Yates Wang, of the Chinese Legation, Washington.

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PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

DECEMBER 4, 1916.

1. Exhibition of Case: DR. J. WHITRIDGE WILLIAMS.

The patient whom you have just seen walk across the amphitheater represents a case of considerable interest in that she sustained a traumatic rupture of the symphysis pubis at the time of labor, and has made a most satisfactory recovery. The history is briefly as follows:

She is 28 years of age. Five years ago she was delivered spontaneously of an eight-pound child. She became pregnant last winter, but was in doubt as to the time of conception. She thought that the last period had begun on December 12, 1915, but was not sure, so that she did not know whether to expect her baby on the 19th of September or a month later. She was registered in the dispensary in the early summer, but nothing abnormal was suspected until she returned on October 20. At that time she had an immensely distended abdomen, and a diagnosis of hydramnios was made. She entered the hospital on October 26, 1916; I saw her the next day and confirmed the diagnosis of excessive hydramnios. Otherwise the examination was not satisfactory, as the child could not be palpated; all that could be felt was what appeared to be a small head which was freely movable in the lower part of the pendulous abdomen.

In view of the patient's discomfort I told Dr. Davis to rupture the membranes, with the idea that premature labor would set in after the escape of the excess of amniotic fluid. Thinking it a simple matter, Dr. Davis turned the manipulation over to one of the assistants, who after several trials reported that he was unable to find the cervix. Dr. Davis then examined the patient with a similar result. When I was told this at my visit the next morning, I examined the patient by the vagina and could find no trace of a cervix, and upon exposing the vaginal vault by means of a speculum I could not see the external os. I then removed the speculum and examined more carefully with my finger, and eventually felt a little ridge extending transversely across the fornix. On making further pressure, the finger passed into a canal which proved to be that of the cervix which had been distorted by the excessive traction exerted by the distended uterus. The membranes were then ruptured and 5 liters of amniotic fluid escaped. Upon re-examining the patient immediately afterwards, I was surprised to find that the condition had materially changed, and that the cervix readily admitted several fingers.

We then debated whether we should leave the patient alone or complete delivery. I decided in favor of the latter, as the patient was already under anæsthesia and was not doing particularly well. Dilatation of the cervix was readily effected by Harris's manual method, and I started to turn and extract the child. Upon introducing my hand into the uterus I was impressed by the large size of the head, and immediately suspected an unusually large or a hydrocephalic child. I carefully palpated a large child through the abdomen, which was now easy, and, after some little hesitation determined to go ahead with the version and extraction and to puncture the head if necessary. The craniotomy instruments were prepared. Version was comparatively easy, although, as soon as the anterior leg had been delivered, I was impressed by its excessive size. Extraction was effected without difficulty and without the employment of undue force. Indeed, I was rather surprised at the ease with which delivery was completed. The child was unusually large and weighed 5600 grams.

After the birth there was a considerable amount of bleeding, and upon inspecting the external genitalia I found a tear to the right of the urethra which extended up into the vagina. Upon introducing the fingers within it I found that the symphysis pubis had been ruptured, and that the ends of the pubic bones were separated by a space which admitted three fingers. After expression of the placenta, several bleeding vessels were ligated and the tear was repaired with catgut sutures, with the exception of a small opening at its lower end through which a drain was inserted. After the usual dressings had been applied, the hips were encased with a 5-inch strip of adhesive plaster. The patient was considerably shocked after delivery; but made an uneventful convalescence, except for a slight rise of temperature for the first few days after delivery. At the end of three weeks she was out of bed and began to walk, and two weeks later could walk as well as she had before the accident occurred. Three days ago I examined her carefully and found that the vulval tear had healed, that there was no trace of rupture of the symphysis, and that no greater motility existed than in a normal puerperal woman. An X-ray examination showed a slight separation between the ends of the two pubic bones, but only a very little more than usual.

I have demonstrated this patient and her baby for three reasons: firstly, because the accident is a rare one; secondly, on account of the very satisfactory results which followed the simple treatment which I have outlined; thirdly, we had to deal with a prolongation of pregnancy. I have seen three other cases of rupture of the symphysis in my experience. One patient died just after delivery, but the other two were treated just as this patient and recovered satisfactorily. The condition is particularly interesting, as it demonstrates the important difference between rupture of the symphysis and fracture of the pelvis. The latter accident is always a serious one, requires complicated treatment and the patient is usually unable to walk for months, whereas, in the former, the treatment is very simple and the recovery prompt.

2. **The Surgical Treatment of Bronchiectasis.** DR. SAMUEL ROBINSON, Mayo Clinic, Rochester, Minn.

3. **The Mechanism and Clinical Significance of Anaphylactic Skin Reactions.** DR. JOHN A. KOLMER, Philadelphia, Pa.

This paper appeared in the May number of the BULLETIN.

DECEMBER 18, 1916.

1. **Studies of the Blood Proteins in Infection and Immunity.** DR. S. H. HURWITZ, San Francisco, Cal.

2. **Is there any Real Analogy between Crown Gall and Cancer? (Abstract).** DR. ERWIN SMITH, Washington, D. C.

1. My first acquaintance with this disease began 20 years ago. At that time it was rather prevalent in peach nurseries in California and in Georgia, from which localities my material was obtained. I worked on the disease about six months without coming to any conclusion as to its cause, but I did not consider the time wholly lost because I reached a definite conclusion that the disease could not be due to insect injuries, to fungi or to slime molds, these being the organisms I had specially in mind. I did not at that time think of bacteria as the cause of the disease, or of the disease as a cancer.

2. Twelve years ago I began on the disease again in conjunction with Dr. C. O. Townsend and Miss Nellie A. Brown. After two years of experimenting we succeeded in isolating the parasite, and published a bulletin from the United States Department of Agriculture on its biology and on the gross appearance and structure of the tumor. Dr. Townsend had then withdrawn from the Department and the whole subject had come into my hands. Even then I thought of it as a cancer (Bull. 213, pp. 161-171).

3. Soon after I discovered the tumor strand and have personally made the other discoveries which seem to connect it with cancer, but have been helped greatly in many arduous labors—inoculations, isolations, preparation of cultures, preparation of sections, etc.—by two assistants who are still working with me, Miss Nellie A. Brown and Miss Lucia McCulloch.

4. Up to this time we have established the following facts concerning this disease:

(a) The bacteria are intracellular. The cells of the host plant are not killed but are stimulated to divide with unusual frequency. The bacteria are not abundant in the cells. They can be cultivated from the tumor tissues by the ordinary methods of the bacteriologists, but cannot be differentially stained within them with any of the aniline stains.

(b) The disease is a hyperplasia.

(c) Secondary tumors are produced.

(d) These secondary tumors are always connected back to the primary tumor by a chain of tumor cells.

(e) The secondary tumors have the structure of the primary tumor; hence the overgrowth is a cancer and not a granuloma.

(f) The common sort of crown gall is developed out of primary or secondary conjunctive tissue. It is, therefore, a sarcoma.

(g) In addition to the proliferating cancer cells, which are quite embryonic, there is a stroma consisting of two types of vessels, which we may liken to the blood-vessels and lymph spaces in animal tissues.

(h) The tumor is sometimes vascularized very abundantly and at other times scantily, according to the greater or less vascularity of the tissue in which it originates.

(i) It is either a hard, slow-growing, long-continued, more or less benign tumor, or a perishable growth quickly invaded by other organisms, and destructive to the plant.

(j) The parasite shows various grades of virulence.

(k) Plants exhibit many degrees of resistance from absolute to slight.

(l) Embryomas. This year it was my good fortune to discover a new type of this tumor in which there are roots, shoots and various embryonic fragments, as indicated in the lantern slides. This type of tumor, to my mind, corresponds strikingly to the most complex animal cancer, that is, to embryomas as they occur in man and animals. [This part of Doctor Smith's paper will appear in full later in the BULLETIN.]

DISCUSSION.

DR. B. E. LIVINGSTON: I should like to ask a question that I think Dr. Smith perhaps may have made clear. I was not quite sure whether this growth went on over long distances after you failed to note your organism. Are we to suppose that the organism gets into the cell, or influences the cell in some way, and that later on the cell can go on for a number of generations plunging out into other tissue in this way without any more of the organism, or do you think the organism goes with it?

DR. ERWIN F. SMITH: Dr. Adami, in one of his letters to me, expressed the idea that while the bacteria might start the primary tumor, the growth could perhaps then go on without them. This I doubt. Growth might go on for a very brief time but not for long because the stimulus would then be exhausted. We have cultivated the organism also from the secondary tumors and once from the tumor strand, so I think we must believe that the organism goes with the tumor. But according to my conception, not one cell in 100 actually has the parasite in it. I conceive cancer in plants to be due to the stimulus exerted by the by-products of the growth of the parasite. These products diffuse out of cells in which they are formed and act on the surrounding tissues.

DR. THAYER: I should like to ask Dr. Smith if he has been able to grow productive growth of this sort by the injection of any products of the bacteria?

DR. ERWIN F. SMITH: I have been able to do this with the products of the organism. These are ammonia, amines, acetic acid, formic acid, etc., that is, substances already shown by Jacques Loeb and others to be among those best adapted to start growth in unfertilized egg cells. These results will be described in a paper which I hope to publish before very long. (See "Mechanism of Tumor Growth in Crown Gall," *Journal of Agricultural Research*, January 29, 1917.)

DR. WINTERNITZ: The ovation Dr. Smith has received expresses our appreciation of his splendid work better than anything I could say. This field of plant pathology, more precisely plant tumors, through Dr. Smith's studies, has been made most attractive and important to these of us especially who are interested in similar problems of human pathology. Unfortunately the latter have not yet reached the happy climax attained in the study of plant tumors.

Tumors of plants are autonomous new growths, they not only do not subserve any useful purpose but ultimately they cause the death of their host. They are, therefore, analogous to human cancer in the broader sense of the latter term. It must be borne in mind, of course, that differentiation and proliferation vary in inverse ratio. The possibility of an abnormal reaction, as the result of an injury, is consequently much greater for the plant with its less highly specialized structure than for the mammal where cell differentiation in some instances attains a stage incompatible with regeneration.

Dr. Smith has produced varied types of tumors by the inoculation of the plant with *Bact. tumefaciens*. Dr. Thayer already has asked whether similar results can be attained with killed cultures, or with chemical products from the bacteria. Dr. Rous, as you know, has succeeded in the production of sarcomata and embryomata of the fowl not only by direct transplantation of portions of similar spontaneous tumors, but also by the injection of cell-free Berkefeld filtrates of emulsions of similar tumors. Comparable results have so far been unattainable with mammalian tumors. It would be interesting indeed if killed cultures or chemical products of the *Bact. tumefaciens* were capable of stimulating neoplasm formation in the plant.

In conclusion, may I ask Dr. Smith in what percentage of spontaneous plant tumors the *Bact. tumefaciens* has been found and whether similar plant tumors can be produced with other organisms or different injurious agents? While, in the last analysis nothing is known concerning the etiology of human cancer, the belief has become more and more general that many different irritants may sooner or later result in tumor formation.

DR. ERWIN F. SMITH: We have plated this organism out of perhaps 30 species of plants belonging to many different families. We do not always get the parasite out, particularly in tumors occurring naturally on the sugar beet. From tumors occurring on this plant naturally we have tried over and over again to get the parasite and generally have failed. I held back the first department bulletin six weeks to get tumors on beets with the organism plated from sugar beets. On the last plate in that bulletin (No. 213, plate 36), slight overgrowths are shown, which was all we could get for the most active of the colonies tested. Since then we have made perhaps 50 sub-cultures from as many hopeful looking colonies and tried these, but failed absolutely. Yet I believe the beet tumor is due to the crown-gall organism. The same is true, to a lesser degree, of isolations from tumors occurring naturally on other plants (daisy, rose, carnation, etc.). The colonies look all right, but frequently they do not do anything when inoculated into the plant. Out of half a dozen colonies selected from the plate as entirely typical, perhaps only one is virulent. I have thought that possibly inside of the tumor some action of the plant goes on which destroys the virulence of the organism. Some strains of the organism certainly lose virulence on media. One of the most virulent daisy strains we ever had lost all power to produce tumors after about three and one-half years on culture media, and yet appeared to be the same organism.

We now have another daisy strain which we have been carrying about three years and a half (called "resistant daisy" because it was isolated from a tumor which appeared by accident on one of our resistant plants). It was extremely virulent at the start and is still moderately virulent, but evidently is losing out. On the other hand, we have carried on culture media for nine years the strain we plated from the California hop, and it is just as virulent as it ever was. One of my assistants and myself have been working for about four years on a paper dealing with the question of crown-gall species, loss of virulence, resistant hosts, etc. We have got enough data to know that there are several distinct strains of *Bacterium tumefaciens*, *e. g.*, the strains isolated from the daisy produce tumors readily on both hop and daisy, but the hop strain crossed on the daisy will not produce any tumors, and so on. We shall be able to show clearly, I believe, that we are dealing with distinct species. We experiment with all kinds of plants. Cancer experiments on animals have been confined to a very few species. I have often wondered why animal pathologists limited themselves to so few kinds of animals. Perhaps failures to cross-graft cancers to other experimental animals have been due to the fact that you have not had the right kind of animal, just as we have tried to inoculate from the hop to the Paris daisy, or from the daisy to the onion, and have had no positive results.

JANUARY 8, 1917.

Several Brief Reports of Current Work from the Department of Pathology by Members of the Pathological Staff.

H-Ion Concentration of Cerebro-Spinal Fluid. (Abstract.) LLOYD D. FELTON.

In work on 76 cerebro-spinal fluids from four groups of patients, normal, senile normal, syphilitic, and epileptic, S. Bayne-Jones, Lloyd D. Felton and R. G. Hussey reported on the H-ion concentration, RpH, refractive index, and Lange's gold reaction as influenced by H-ion concentration. It was found that previous workers had not taken into consideration the unstable CO_2 tension, thus reporting results clearly erroneous. By examining the fluid immediately after withdrawal (as did Bisgaard), the H-ion concentration of the 76 fluids averaged 7.7, there being no characteristic change in any of the diseases studied. The RpH ranges from .6 to .9. Refractive index was found to be between 1.3348 and 1.3351, confirming the work of Babe. Lange's gold reaction was not influenced by the H-ion concentration.

The Oxygen Pressure Necessary for Cellular Activity. (Abstract.) MONTROSE T. BURROWS, M. D.

In an early study the author had noted that the oxygen necessary for cellular activity in a tissue culture comes from the air-

chamber of the hollow ground slide in which the culture is suspended. The cultures were made by placing a small fragment of tissue, 1 mm. in diameter, in a layer of plasma on the surface of a cover-glass. The cover-glass is inverted over a hollow slide so that the medium and tissue hang in the air-chamber. The cover is sealed to the slide with vaseline and paraffine to prevent drying.

In the present study a special type of culture has been constructed. It is so arranged as to allow one to pass into it any gas or combination of gases. The air-chamber of this culture is large, 40 to 60 times that of the ordinary culture in which growth may continue actively for several days. This culture chamber is made from one piece of glass and it can be sealed by fusing. The effect on the growth of the cells of pure oxygen and partial pressure of oxygen have been tested. The partial pressures of oxygen were obtained by diluting pure oxygen with the nitrogen gas. The tissues used have been fragments of heart muscle and skin of chick embryos and fœtal chickens. The medium is blood plasma, prepared from the blood of adult chickens. There is a small error in the measurements of the partial pressure of oxygen.

Including this error the results have been considered interesting. The cells grow actively in pure oxygen. The growth, although in some instances possibly slightly more rapid, is not greater in an atmosphere of pure oxygen than that observed in an atmosphere containing 9 or 10 per cent of oxygen. A small growth is seen when the partial pressure of oxygen is as low as 6.6 per cent, 45.6 mm. of mercury, an oxygen pressure not far removed from the known venous oxygen pressure of man. We do not know the venous oxygen pressure of the chicken.

The Interrelation of the Surviving Heart and Pancreas of the Dog in Sugar Metabolism. (Abstract.)

ADMONT H. CLARK, M. D.

The experiments indicate that the pancreas when perfused aseptically with Locke's solution containing physiological concentrations of dextrose, does not alter the reducing properties of the perfused solution. The pancreas, however, seems to supply something to the Locke's solution circulating through its arteries which in some way brings about a utilization of sugar by the living heart to an extent that does not occur with the heart alone. This pancreatic substance possesses some of the characteristics of an enzyme. It is inactivated by boiling; it is unstable, rapidly becoming inactive on standing; it acts in small amounts; it causes a great acceleration in the rate of a reaction which otherwise proceeds slowly, and the rate of reaction diminishes as the reaction proceeds. Thus this substance has more of the characteristics of an enzyme than of a stable internal secretion like that of the adrenal glands. The disappearance of sugar was dependent upon the presence of living heart tissue, and it ceased as soon as the perfusate was removed from the heart-pancreas circulation and did not occur at all when a pancreatic perfusate was passed through a non-beating heart. This result indicates that the reaction is not similar to that obtained when muscle and pancreas extracts act on more concentrated solutions of dextrose.

The living heart, in the presence of the pancreatic factor and dextrose, is responsible for two effects: First, a condensation of the sugar to a non-reducing form that yields again a simple sugar on hydrolysis or by simply standing, with a preservative at 37° C. for 24 hours; second, a disappearance of sugar which is probably due to its destruction by hydrolysis or oxidation. After deducting the reducing sugar in the heart-pancreas perfusions which could be recovered by hydrolysis, the amount of sugar which had actually disappeared exceeded that which was used by the heart when perfused with dextrose alone. As to the fate of this portion of the sugar, no definite evidence was obtained.

The question arises as to whether this substance obtained from the perfused pancreas is identical with the hypothetical internal secretion of the pancreas so essential in sugar metabolism. That there is an internal secretion of the pancreas which can be obtained by this method, and that in some way it accelerates the utilization of sugar by the living heart, seems evident. Though the conclusions are based on the heart and pancreas isolated from the numerous interrelating factors occurring in the body, the evidence suggests at least that the substance or substances obtained by perfusing the pancreas may be concerned in the normal activity of the pancreas upon sugar metabolism.

Anatomical Changes Associated with High Cholesterin Diet. (Abstract.)

H. C. SCHMEISSER.

In The John Hopkins Hospital Bulletin, January, 1916, Knox, Wahl and Schmeisser published studies of two cases of Gaucher's disease.

These cases were characterized anatomically by a marked enlargement of the spleen, liver, kidneys, adrenals and to a less degree the lymph glands. Each organ had a characteristic appearance.

The increase in the size of the organ was brought about, as could be seen microscopically, by the presence of a large pale cell with a round or oval, semivesicular or deep-staining nucleus and a granular or finely vacuolated cytoplasm. Similar changes frequently involved the parenchymatous cells.

The all important question was to determine the nature of the material in the cytoplasm of these cells.

Some preliminary microchemical tests and the application of the crossed Nicol's prisms led to the belief that it might be of lipoid nature.

Consequently Wahl and Richardson undertook a chemical study and concluded that it was lipoid.

In the meanwhile I attempted to produce this disease experimentally.

A number of investigators, and more recently Bailey, have shown that the feeding of lipoid-rich substances, as for instance egg-yolk or brain, or pure cholesterin to rabbits produces a deposit of anisotropic fat in various organs.

Making use of this fact, rabbits were fed with large amounts of hog's brain over a long period of time. This resulted in the production of a picture which both grossly and microscopically closely simulates the anatomical findings in the two cases reported as Gaucher's disease.

DISCUSSION.

DR. F. A. EVANS: I had the privilege of studying some of the cases Dr. Mandlebaum admits as Gaucher's disease, together with some slides of Dr. Schmeisser's case, and the cells are certainly different. Whether one is justified in accepting the limitations Dr. Mandlebaum imposes on the diagnosis, Gaucher's disease, is of course open to question, but it is undeniable that the cells in the two cases differ not only in distribution but in morphology. That raises the question as to what were the cells in this case. Are they the same cells as those seen in Dr. Mandlebaum's cases in reaction to different stimuli, or the same cells in different stages of reaction to the same stimulus? In talking this matter over with Dr. Oskar Klotz, he called my attention to the results of some experiments done in his laboratory. In these, cholesterin was injected into rabbits, and a pathological picture obtained apparently the same as that in Dr. Schmeisser's feeding experiments. Some animals were allowed to live after the injections were stopped, and the cells changed their form and reproduced practically the picture of the cells that Dr. Mandlebaum considers typical of Gaucher's disease, the only difference being in the distribution. Did Dr. Schmeisser let any of his animals live after the cholesterin feeding was stopped, and if so, what was the pathological picture?

The Blood-Vessels of the Heart Valves. (Abstract.) Dr. S. Bayne-Jones.

By injecting neutral carmin gelatin at 45°C. into the coronary arteries under a pressure of 160 to 190 mm. Hg., blood-vessels were demonstrated in the arterioventricular and semilunar valves of normal human hearts. The arteries to the mitral and tricuspid valves are distinct branches of the annular divisions of the coronary arteries. These vessels pass down the thicker regions of the valves and ramify in a glomerular-like arrangement along the line of closure of these valves. The chordæ tendineæ receive a few small blood-vessels from the arteries of the papillary muscles. The semilunar valves receive delicate arteries from the vasa vasorum of the aorta and pulmonary arteries and from the blood-vessels of the auricular endocardium.

These studies extend the findings reported by Luschka in 1852 and 1863 and of others who have shown that the normal heart valves are vascularized. The difficulties of the technic are considerable, but when the factors are properly arranged, the blood-vessels of the heart valves can be injected with regularity. The results of these studies give an anatomical basis for the conception that endocarditis may be embolic in origin.

Experimental Nephropathy in the Dog. Lesions Produced by Injection of the Bacillus Bronchisepticus into the Renal Artery. (Abstract.) M. C. Winternitz.

Spontaneous renal lesions are not uncommon in the dog. As a rule they are inconspicuous, but occasionally extensive anatomical changes occur similar, even in their detail, to those found in the human kidney in the progressive, non-suppurative types of nephritis.

The etiology of the disease in the dog is as obscure as it is in man; and it is evident that the two conditions may result from similar causes, and that the great majority of chemical irritants already used for the production of experimental renal lesions can have no more place in the etiology of these spontaneous changes in the dog than they have in the pathology of the human kidney. Promising experimental results have been obtained recently with bacteria as the exciting agent, and this is in accord with the growing impression that microorganisms may be etiologically associated with the more important types of progressive nephropathies in man.

Assuming this impression to be correct, it is probable that the nephropathy of the dog is the result of some acute infectious disease frequent in the species. Accordingly, in the experiments here recorded, the attempt to produce a progressive nephropathy in the dog similar to those of man differs in method from the usual procedures, in that a microorganism, the bacillus bronchisepticus, known to produce spontaneous disease in the species, has been employed.

The organism used for injection corresponded in its microscopical characteristics, staining qualities, cultural reactions and pathogenicity for lower animals to the bacillus bronchisepticus.

About 5 c. c. of either a 36- to 48-hour growth in litmus milk or of an emulsion of a growth, from an agar slant in sterile salt solution, were injected directly into the renal artery. At first both, later only one kidney was injected. The remaining one was subsequently similarly injected, or removed after the acute symptoms following the initial procedure had subsided.

All operations were done under ether anesthesia and with complete surgical asepsis.

The immediate results of this procedure varied markedly. Some of the animals showed definite generalized distemper, with conjunctivitis, nasal discharge, anorexia and loss of weight. Their urine at first contained some blood and showed large amounts of albumin. On the other hand, other dogs showed no signs whatever of general infection, and after the first few days only the slightest traces of albuminuria. The larger number of animals reacted to the injection definitely, but without the severe generalized infection of the first group. It seems reasonable to explain these results on the ground of variation in susceptibility of the different animals. The severe, overwhelming infections occurred, as a rule, in young dogs, while those showing practically no reaction were old, or had at least attained their full growth. This coincides with the well-known immunity which commonly follows an attack of distemper:

It is possible, therefore, to divide the animals into three groups.

(1) Immune animals that showed only a transient renal lesion and no general reaction.

(2) Animals that died acutely with a fulminating renal lesion and an acute general reaction.

(3) Those which showed a milder renal lesion which progressed after the less severe, general reaction had subsided. In this last group the animals ultimately succumbed to renal insufficiency, provided the uninjected kidney was removed shortly after the acute stage had passed.

JANUARY 22, 1917.

1. Exhibition of Case. Dr. T. M. Rivers.

To appear later in the Bulletin.

2. Demonstration of an Apparatus for Taking Continuous Blood Pressure Tracings in Man. (Abstract.) A. C. Kolls.

It is a well-known fact that the pressure in a cuff, inflated to the point at which pulsations in the distal portion of the artery are just obliterated, is equal to the maximum intra-arterial pressure. It is also well known that a sphygmograph which has been connected to another cuff placed below the first one gives an objective method for determining the point at which the pulse is obliterated. The author has made use of these facts and, by automatically forcing air into the upper cuff when the sphygmograph is actuated and allowing air to flow out when the sphygmograph is at rest, has obtained graphic records of the systolic pressure.

Observations are made by placing the two cuffs upon the subject's arm and connecting them so that the lower one may be inflated from the other in order to insure good transmission of the pulsations to the sphygmograph. The communication between the two cuffs is closed when sufficient pressure has been made in the sphygmograph system. The upper cuff is connected with a recording mercury manometer and an electromagnetic device of such design that a valve is opened to a head of pressure (a large bottle which is pumped up at intervals with a bulb) when the circuit is completed and closed when the circuit is broken. Synchronous with the closing off of the head of pressure another valve establishes a communication between the upper cuff and the outside air so that the pressure slowly falls. Thus, when the intra-arterial pressure is higher than the pressure in the upper cuff, pulsations reach the second cuff and actuate the sphygmograph, which breaks a relay circuit and this in turn closes the circuit to the electromagnet, opening the valve between the head of pressure and the cuff. In case the intra-arterial pressure is lower than the pressure in the upper cuff, the sphygmograph is at rest and air slowly escapes from the valve just mentioned. These changes of pressure are recorded on a moving drum by the mercury manometer.

Tracings may be taken for periods exceeding five minutes without marked discomfort to the subject. Observations have been made for 20 minutes without interruption. However, the pressure in the cuffs may be relieved at any time and again brought back to systolic pressure, thereby giving the subject a brief period of relief. Determinations at intervals with the Tycos instrument on the other arm varied only a few millimeters from the calculated pressure as registered on the graphic records.

3. Shock at the Front. Dr. W. T. Porter, Boston, Mass.

THE LAENNEC SOCIETY.

JANUARY 29, 1917.

Chronic Non-Tuberculous Lung Infections. DR. A. H. GARVIN.

Before I take up the subject of my talk, I should like to show you some X-ray pictures of localized lung miliary tuberculosis, and to call your attention to the sequence of pathological event in these cases. It seems that we are just beginning to have an idea of the sequence of pathologic event that occurs in lungs infected by the tubercle bacillus. There stands out some new work, however, and some old facts which may be profitably reviewed with a new explanation in mind; that an individual or animal infected with the tubercle bacillus for the first time reacts entirely differently from the type of reaction occurring when infected the second time. This change of circumstances is not a generally recognized phenomenon.

It seems to be the truth that general miliary tuberculosis is almost never diagnosed. The same is more conspicuously true of localized miliary tuberculosis. The only one perfectly familiar with miliary tuberculosis is the pathologist. Two recent case histories where in one case the lung was noted to contain but a few râles at the apex, showed an extensive miliary tuberculosis at autopsy soon afterwards performed, and in another case the lungs were noted to be perfectly free. In a very short period however, the pathological picture of a lung riddled with the ordinary type of crude tubercle was made evident at the autopsy table.

This almost routine failure to make a diagnosis of miliary tuberculosis in life is conspicuous.

Koch was the first who noted in animal experiment that a second infection with the tubercle bacillus did not progress in the same sequence as the first infection, but tended to remain stationary and to heal. He was followed by other investigators and finally Paul Roemer added much in the detail protocol where animals were infected with varying relation of doses, of culture, of virulence, and of interval between first and second infections, adding much to the present knowledge of the genesis of phthisis as it is met with clinically.

Trudeau was the first in this country to appreciate the relationship of altered reaction and course of disease in animals that received a first and second infection and his work was extended in detail by Doctors Nichol, Allen, Baldwin and later Dr. Krause. Dr. Krause has coordinated particularly the variables that relate to type of first infection, to time interval and to type and size of second infection. This work has been made possible by the possession of old and well-pedigreed strains of bacillus R_1, H_{37}, and B_1.

The important point in this animal experiment work is the development of an acute pulmonic miliary tuberculosis of a type that can be classified as crude Laennec tubercle type, which is easily recognized by the naked eye and the subsequent complete disappearance of this crude Laennec miliary tuberculosis. The development of, and the disappearance of, this crude Laennec miliary tuberculosis is dependent upon the type of first infection and the interval intervening before the second hematogenous infection is given. The miliary tuberculosis, when the inoculation dose is the second dose, is miraculous both in its development and in its disappearance.

The first clinical bearing of this animal work, of course, is to demonstrate the existence of it in the patient. General miliary tuberculosis does not adequately illustrate, but it is of interest when the miliary tuberculosis is localized either to both lungs, to one lung, or more illustrative still when limited to the small anatomical divisions of the lung; namely, a lobe, or part of a lobe. It is still of greater interest if such a localization can be demonstrated and further demonstrated to disappear after occurring.

There is no doubt that this clinically happens. The point of being aware of it when it is taking place is an entirely different matter. If it can happen in the animal, as conclusively as Dr. Krause's experiments illustrate, there is no reason why it should not be expected to happen in the human being. Here also it seems to be true that the diagnosis of localized pulmonic miliary tuberculosis escapes.

The brief case stories I present illustrate: that localized pulmonic miliary tuberculosis occurs as follows: in one lung; in one lobe, in part of one lobe; and in one case of one lobe miliary tuberculosis is illustrated the disappearance of a one lobe localized miliary tuberculosis.

(X-ray plate demonstration with brief case histories.)

CHRONIC NON-TUBERCULOUS LUNG INFECTION.

A report of nine cases of lung inflammation simulating tuberculosis in clinical story and physical examination, where the diagnosis was first confused with tuberculosis.

Etiology.—A study of the sputum flora, seems to point to the probable cause of the disease by the common secondary sputum organisms, the influenza bacillus being found most frequently, the pneumococcus, streptococcus, and in one case an undetermined Gram negative bacillus.

The time in all cases averaged about four years before the condition was certainly differentiated from tuberculosis. The clinical course simulated tuberculosis quite regularly, in that the patients suffered from varying types of increasing cough and expectoration with occasional periods of loss of weight, chills, night sweats, and, not infrequently, hemorrhages.

Physical examination showed a predominance of lesions in the base of the lung, and in cases where no lesion could be discovered, the examination of the patient in the inverted position after lung drainage for 15 minutes would often reveal a base lesion that otherwise would have been missed. Apex cases require longer time for differential diagnosis than base cases. The differential diagnosis is easiest in base cases because the state of health is usually better than would be expected for the duration of the disease and the extent of lesion, the number of physical signs and the effect of posture on their increase.

The differential diagnosis from bronchiectasis is usually not difficult.

Treatment is posture in one or another type of inverted position to be carried out sufficiently long at each period to thoroughly cleanse the very residual sputum from the respiratory tract. If the treatment is persisted in thoroughly 15 minutes, four times a day, all retension symptoms are relieved and the patient rapidly improves in general health.

Studies were carried out to determine the danger of such secondary organism carriers to neighboring tuberculous patients, with the result that the ordinary cough sputum prophylaxis seems to be sufficient to avoid any carrier danger.

DISCUSSION.

DR. AUSTRIAN: So far as I am aware we have never recognized such a condition here as localized pulmonary miliary tuberculosis. Probably we have never looked for it. Patients return with symptoms such as Dr. Garvin describes, but we do not take X-ray pictures of their lungs at those times. One has to be prepared to accept absolutely the belief that the X-ray picture in these cases that have been demonstrated is proof that the lesion is tuberculous. Dr. Garvin in some instances did speak definitely of cases that have not been proved to be tuberculous. In one or two instances the tubercle bacillus had not been demonstrated, although the patients were recognized as having a long-standing tuberculosis.

We do see many non-tuberculous lung infections. Some it has not taken four years to diagnose and some it has taken longer.

I can truly say it has taken much more than four years to give relief to them. I recall one patient who has been around the dispensary for seven years, a woman with a typical clinical non-tuberculous infection, who goes through periods of exacerbation and relief and who in addition to cough has large amounts of sputum and some hemoptysis. We have never tried postural treatment with her.

We have been much interested this year in finding at least two cases of infection of the lower lobe with no evidence of disease elsewhere, the chronic non-tuberculous type. Another patient came in this morning, an employe of the hospital, whom we have been watching for four years, whose general condition remains excellent, but who has had persistent cough with large amounts of sputum, and some hemoptysis. I do not recall how many sputum examinations we have made, but we have never found the tubercle bacillus.

We certainly would like to put the patient through treatment with the postural method, but in our out-patient department this may be impracticable; when they get into their homes, I am afraid they would not carry it out. I imagine that with intelligent cooperative patients, under proper conditions of control, one could accomplish considerably more.

From the chronic non-tuberculous lung infections we have isolated various organisms. We have found the streptococcus mucosus in one group, the pneumococcus in another. From a small number we isolated the influenza bacillus in pure culture from the sputum.

At least one of these chronic lung infections has shown a varied flora—on one occasion a pure culture of pneumococcus was grown from the sputum; later a streptococcus mucosus was isolated; again a mixed culture of the two, and at another time the influenza bacillus appeared. Inasmuch as these findings were obtained in the period when vaccine treatment was considered worthy of a therapeutic trial, this patient proved to us a veritable bug-bear.

Dr. Garvin's interesting paper has indicated the value of periodic roentgenoscopic examinations of patients with pulmonary tuberculosis and has outlined a therapeutic procedure that should prove of great efficacy in the management of chronic non-tuberculous infections of the lungs.

Dr. Gordon Wilson: These cases of non-tuberculous lung infection have always been of interest to me on account of the absence of the usual toxic symptoms. Although the patients frequently have an evening temperature, there is no loss of strength, and no lassitude. Another point is the somewhat characteristic change in the breath sounds. You do not notice the intensification of the breath sounds and the râles are extremely characteristic. They have a sticky quality that you hear in no other lung condition.

Dr. Leutscher: Some years ago everything of a chronic nature was assumed to be tuberculosis. I have been impressed with a number of cases of cough in students following attacks of measles. There was probably some pulmonary infection at the time of the measles, with possibly some lung defect which had persisted ever since. I have followed some of these cases for a number of years now, and the condition has not changed very much. The type of organism varies. I think we found the influenza bacillus mainly in the bronchiectasis cases. Pneumococci and streptococci were found in some of the other cases. As to the type of organism, it seemed there might be one organism at one time and another at another time. Some of our patients have been followed over a number of years, but they have always had the same type of organism, not only so far as smears were concerned but as regards cultural reactions. In some of our cases which were followed as long as seven years the tubercle bacillus could never be found, but there was always a definite organism which could account for the infection.

Dr. Boggs: Some cases in this group are especially interesting to me as in the last few years Doctor Pincoffs and myself have done some work on mycotic infections. We feel we must look to the sanatoria especially for the working out of this field, and that examination of the case that is not clear cut should include the thought that there may be a mycotic infection. Our experience has been that the gross examination of the carefully collected sputum is important. Plating is done between glass plates, and by means of the low power microscope the little nodules are picked out and planted in such material as acid carbohydrate media, to give special encouragement to the fungi and discouragement to other forms of bacterial growth. We have collected quite a number of such mycotic cases. I am not speaking now of the streptothrix type, but of the larger, grosser bodies which grow luxuriantly in carbohydrate media, especially in acid media. Some of these cases have been in no sense chronic, but somewhat acute and rapidly fatal. Others are chronic and are mistaken for tuberculosis.

The types of these organisms that we have had to work with have been very similar. We are not sufficiently sure of our mycology to say what they are exactly, but they belong to groups that are certainly very distinct from the streptothrix. They are more like some of the spores that have been described lately by Meyer of San Francisco. We do feel that there is work to be done in the careful examination of the sputum, of the chronic as well as the acute pulmonary cases, with the specific object of finding out whether or not fungi are present that are not made out under ordinary methods. Many of these forms are quite unrecognizable in stained specimens. One must use cultural methods and the advantage of culture in the way I have indicated must be remembered.

Dr. C. A. Penrose: I would like to mention in connection with these chronic coughs, the prevalence of cough, with râles and bronchitis, in so many cases of gall bladder infection I have seen. Dr. Cullen has asked me to look out for this in a number of these cases, and in about 50 per cent we have found the chronic cough with profuse expectoration and râles. I think the question of a reflex condition should be considered in these chronic cough cases.

Dr. Krause: I was greatly interested in Dr. Garvin's pictures showing tuberculosis healed to such an extent that it did not produce a shadow. Several years ago Dr. Soper and I started some experiments with the idea that tuberculosis that went on to degeneration certainly must leave its scar. We reinfected a number of animals by inoculation into the mesenteric veins and killed them in series. Although all the animals that were killed showed a great deal of tuberculosis in the liver during the first three, four or six weeks, we found that at about the seventieth or eightieth day we were dealing with smooth livers. In other words the tuberculosis had disappeared, and even microscopically there was no trace left. I think several of you were here in the spring when I showed some specimens of tuberculous reinfected animals in which the process had gone on to caseation, and after the sixth, seventh or eighth week there was a great deal of normal lung tissue compared to what had been the case a few weeks earlier.

The point Dr. Wilson made is well-worth bearing in mind, particularly for the student who is doing chest work. I have always thought that one of the best general impressions with which to approach a diagnosis of lung disease was that given the same amount of anatomic change, non-tuberculous lung infection is not so likely to give you so marked a picture of constitutional disturbance as active tuberculosis. In non-tuberculous pulmonary disease it is more usual to have the focal symptoms dominate the field; in tuberculosis, the constitutional symptoms are usually in the foreground. It is of course all important to remember that localized pulmonary tuberculosis is almost always apical, whereas chronic non-tuberculous lung disease is generally basal. In arriv-

ing at a diagnosis we should give such general impressions and the law of averages their proper weight. They will put us straight more often than lead us astray.

DR. JANEWAY: We are all indebted not only to Dr. Garvin, but to the various gentlemen who have discussed this paper, for bringing out the various types of lung disease that one never thinks of until his attention has been called to them. One important lesson for all of us is this—that we must not look at sputum as a substance in which we do or do not find tubercle bacilli, but as a means of making an etiological diagnosis. That diagnosis ought to be pressed far beyond the point of whether tuberculosis is or is not present. The great mistake made by most physicians, is that they fail to feel the necessity for making a diagnosis, if they can only exclude tuberculosis.

DR. GARVIN: I do not know how best to answer Dr. Austrian as to whether or not these cases presented as localized pulmonic miliary tuberculosis are tuberculous. That would need a long discussion; but from the photographs of each, together with knowledge of the clinical histories, I feel sure they are tuberculous; most of them have been sputum positive for brief periods. It is perhaps not absolutely proven in one or two, but the manifestations they show clinically can be only those of tuberculosis.

With the mycotic type of infection I have had no experience at all, perhaps because I have overlooked it.

The point I wish to repeat is the method of treatment of the non-tuberculous cases. I feel that this can be carried out even with dispensary patients if the patients get the point of the treatment and really appreciate it. At first, standing on their heads, as it were, seemed to the patients in this series, ridiculous, but after one or two patients began a remarkable improvement, the performance of posture ceased to be a novelty and patients were perfectly willing to follow directions and improve upon the procedure.

NOTES ON NEW BOOKS.

War Surgery. By EDMOND DELORME, Médicin Inspecteur Général de l'armée. Translated by H. DE MÉRIC. Cloth, $1.50. (*New York: Paul B. Hoeber, 1915.*)

An excellent summary of the principles of war surgery embodying the observations of the author and other French surgeons in the present war. The author takes up in the first chapter the types of projectiles, the differences in wounds made by the different varieties of missiles and the various modifications of bullet wounds, which can be explained by differences in velocity, ricochet and turning over of the bullet in the tissues. In every war there has always been a charge by both sides that the opposing forces were using dumdum or explosive bullets. Similar charges were made by our own surgeons during the Spanish war, and at the onset of the present European war by both sides. The author emphasizes the explosive effects on tissues of short-range shots and ricochets causing the terrible mutilating wounds which surgeons, inexperienced in gun-shot injuries, are liable to attribute to dumdum and explosive bullets. No attempt is made to give the technique of the various operative procedures, but the general indications for operation are well explained. The book is especially valuable in that suggestions are given for the management of the various injuries from the time the patient has been wounded on the field until his reception in a permanent base hospital. The types of cases which should be kept as near the front as possible and those which it is permissible to withdraw with safety are emphasized. The general principles of treatment are excellently given. Not enough emphasis is placed on the early and routine injection of antitetanic serum, nor is there any mention of the value of continuous irrigation or of the excellent results obtained by Carrel with Dakin's solution. The chapter on fractures is brief but very valuable, as the management of these cases is taken up from the first dressing. Delorme is an ardent advocate of his own metallic perforated splints which can be easily bent into the proper position for correcting deformities. There is little mention of the great value of extension, especially in fractures of the femur, and the various ingenious means by which extension and coaptation of the fragments can be obtained, while at the same time permitting easy access to the wound. In the treatment of abdominal wounds the author believes that operation should be "considered as only an exceptional method" and he is in favor of the Murphy suprapubic incision with simple drainage of the pelvis. In general Delorme has been impressed by the value of conservative measures as far as possible, save in the treatment of beginning infection where he vigorously emphasizes the importance of wide incision.

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